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## THE AUTONOMIC NERVOUS SYSTEM IN RELATION TO ALLERGY

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THE common manifestations of allergy, such as hay fever, asthma and eczema, and diverse anaphylactic reactions probably are invariably associated with abnormal functional states of the autonomic nerves. The latter may be induced by the tissue reactions to the sensitizing agent in question, but not infrequently the modified functional status of the autonomic nerves is a factor in the etiology of allergic disease. The so-called "allergic state" probably does not exist in the presence of a normal functional status of the autonomic nerves.

### NATURE OF THE ALLERGIC STATE

The nature of the allergic state as yet is obscure. A hereditary factor undoubtedly exists in many cases. The observation of Landsteiner and Chase<sup>23</sup>, confirmed by Jacobs, Kelley and Sommers<sup>22</sup>, that a strain of guinea pigs which is resistant to a given allergen may be obtained by selective breeding strongly supports this point of view. The hereditary factor may be concerned with the capacity of the organisms to produce tissue antibodies, the permeability of the tissue elements, including the capillary endothelium, or the release of substances such as histamine and acetylcholine, all of which processes may be influenced through the autonomic nerves.

Emotional factors in the etiology of allergic disease have long been recognized. These factors have gained increasing recognition, during recent years, in the causation of various allergic disorders. As Gillespie<sup>14</sup> pointed out, an asthmatic attack may occur as the accumulation of an anxiety, the

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expression of an emotional conflict, a protest against an unwelcome situation, a means of escape or as a conditioned response. Urticaria of emotional origin is not uncommon. Abramson<sup>1</sup> reported the case of a woman aged thirty-one who, while suffering from certain mental conflicts, developed giant hives after swimming in cold water. The application of ice to her arm also resulted in the development of an urticarial wheal. When later her mental conflicts were adjusted her sensitiveness to cold disappeared. Numerous cases in which allergic symptoms of other types have been precipitated by emotional disturbances have been reported.

The emotional factors in allergic disease emphasize the role of the central autonomic centers, particularly those located in the hypothalamus. In a review of the nature of eczema, Milian<sup>26</sup> advanced clinical data in support of the assumption that the itching associated with this disorder is of central origin and that the associated capillary dilatation, edema and secondary vesiculation are related to abnormal vasomotor function due to the low threshold susceptibility of these nerves to itching. Lortat-Jacob<sup>25</sup> also demonstrated definite association of the sympathetic nerves and pruritis, erythema and vesiculation in the background of contact allergy. He cited the case of a woman with more or less generalized eruption, caused by working with synthetic vanilla, which was aggravated by pilocarpine and relieved by atropine. The cutaneous lesions in this case obviously were related to reflex activity mediated through central autonomic centers.

The most spectacular of all allergic manifestations, protein anaphylaxis, undoubtedly represents the results of the antibody-allergen reactions of the tissue elements. Certain allergic manifestations, e.g., those of physical allergy, cannot be explained on the same basis. A combination of heat, cold or sunlight with body proteins which could produce a new protein is inconceivable. In either case the functional disturbances bear essentially the same relationship to the autonomic nerves. They involve primarily tonic changes in the musculature of the visceral organs, including the vascular system. Since the tonus of the visceral musculature is regulated through the autonomic nerves, deviations from the normal tonic level of the visceral organs imply deviations from the normal functional autonomic balance. The changes in smooth muscle tonus commonly associated with allergic disease, e.g., the heightened tonus of the bronchial musculature in bronchial asthma and the increased gastro-intestinal tonus and motility associated with various allergic diseases, indicate heightened parasympathetic activity. The decreased vascular tonus, particularly in the shock tissue, commonly associated with allergic reactions are of the same order, although the efferent innervation of most of the blood vessels is mediated solely through sympathetic nerves. The decreased vascular tonus may be explained in part on the basis of decreased activity of the adrenergic vasoconstrictor nerves and in part on the basis of increased activity of the cholinergic vasodilators. The increased secretory activity associated with allergic catarrhal inflammation of the nasal, pharyngeal and bronchial

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mucous membranes, the gastro-intestinal mucosa and the conjunctivae also indicate exaggerated parasympathetic tonus. The vasodilatation of the mucous membranes, indicating corresponding activity of the cholinergic vasodilator fibers, results in increased permeability of the capillary bed, which facilitates the discharge of serous fluid, thus providing the substratum for increased secretory output of the glands. Increased capillary permeability due to vasodilator stimulation, in the absence of allergic disease, has been amply demonstrated. Activation of the glands in the mucous membranes is mediated mainly through the parasympathetic nerves. Some of the most characteristic manifestations of allergic disease, therefore, are causally related to heightened parasympathetic or cholinergic reactivity.

Hyperreactivity of the cholinergic autonomic nerves associated with anaphylactic reactions in animals, in the absence of a pre-existing autonomic imbalance, has been amply demonstrated. In experiments on cats reported by Heim<sup>16</sup>, the intravenous injection of a serum to which the animals had been sensitized three to five weeks previously resulted in a marked increase in parasympathetic tonus and reactivity of the parasympathetically innervated tissues.

The localization and the limitations of the shock tissue present intricate problems which probably will find their solution in a more complete understanding of the role of the cholinergic autonomic nerves in allergic reactions. The discharge of nerve impulses through the sympathetic nerves, particularly when they emanate from higher autonomic centers such as those located in the hypothalamus, is diffuse and influences the entire body. This mode of action is one of the most significant aspects of sympathetic function. The high efficiency of the sympathetic nerves in effecting adjustments to external and internal environmental factors can be explained most satisfactorily on this basis. Totally sympathectomized animals may continue to live without apparent functional deficiencies while they are not subjected to conditions of physiological stress but they are unable to effect adequate adjustments to changes in temperature or to maintain the environment of the tissue elements in a constant state. Homeostasis is mediated primarily through the sympathetic nerves. The discharge of impulses through the parasympathetic or other cholinergic nerves is less diffuse and may be limited to a single organ or body region. This undoubtedly provides the physiologic basis for the fact that allergic reactions, as observed clinically, commonly occur in localized tissues known as shock tissues. The cholinergic influence in these reactions is indicated by the fact that, regardless of which shock tissue is affected, adrenin affords relief. The general adrenergic reaction tends to counteract the effect of the local cholinergic stimulation, wherever the disturbance may be. The experimental observation that the blood of rabbits in anaphylactic shock contains relatively large quantities of acetylcholine, whereas that of normal control rabbits contains none, supports this point of view.

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### AUTONOMIC IMBALANCE

If the assumption that allergic reactions are constantly associated with a shift in the autonomic functional balance in favor of the cholinergic nerves may be regarded as well founded, the means by which changes in the functional autonomic balance may be detected deserve careful consideration. Therapeutic measures designed to restore normal autonomic balance also deserve consideration in the treatment of allergic disease.

The original concepts of sympatheticotonia and vagotonia formulated by Eppinger and Hess obviously require revision. In the light of our present knowledge of the humoral transmission of nerve impulses and the distribution of cholinergic and adrenergic fibers in both divisions of the autonomic nervous system, the concept of a clear-cut functional difference between the parasympathetic and the sympathetic nerves is untenable. On the basis of this knowledge and the results of a study involving measurements, over an extended period, of twenty physiological variables of which at least twelve are mediated at least in part through the autonomic nerves, in sixty-two children six to eleven years of age, and a factor analysis of these data, Wenger<sup>32</sup> has proposed the following restatement of the theory of Eppinger and Hess:

(a) "The differential chemical reactivity and the physiological antagonism of the adrenergic and cholinergic branches of the autonomic nervous system permit of a situation in which the action of one branch may predominate over that of the other. This predominance, or autonomic imbalance, may be phasic or chronic, and may obtain for either the adrenergic or the cholinergic system. (b) Autonomic imbalance, when measured in an unselected population, will be distributed continuously about a central tendency which shall be defined as autonomic balance."

### CRITERIA OF THE AUTONOMIC FUNCTIONAL STATE

A test of autonomic function can be significant only if it indicates clearly whether an observed reaction is due to increased or decreased activity of either the adrenergic or cholinergic nerves. Tests which merely indicate a functional imbalance are of little value and may even be misleading, since they do not define the reaction in question in the neural and neurohumoral systems.

Circumvention of the difficulties in interpreting observed autonomic reactions in terms of neurohumoral processes has been attempted in various ways: (1) by recording the reactions of mechanisms which are innervated through only one division of the autonomic system, e.g., the nictitating membrane; (2) by elimination of either the sympathetic or the parasympathetic innervation of the organ in question; (3) by assaying *in vivo* or *in vitro* the neurohumoral mediator liberated; (4) by recording the action potentials of the respective autonomic nerves; (5) by analysis of the reactions to appropriate pharmacologic agents. All of these methods have been found useful but the interpretation of the results obtained is beset

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with difficulties due to the tendency of autonomic reactions to bring about adaptive changes and to maintain the constancy of the internal milieu.

The tests which probably will be found most useful in the study of autonomic functional changes associated with allergic disease are those which involve reactions to pharmacologic agents. In general, individuals with exaggerated sympathetic tonus react more strongly to sympathomimetic agents than those with normal autonomic balance. Individuals with exaggerated parasympathetic tonus likewise react more strongly to parasympathomimetic agents than those with normal balance. The effect of a given dose of a drug like ergotamine, which tends to block the sympathetic or adrenergic nerves, or atropine, which tends to block the parasympathetic or cholinergic nerves, therefore, varies according to the functional balance of the autonomic system. In the presence of exaggerated sympathetic tonus a larger dose of ergotamine is required to block adrenergic function than in the presence of normal autonomic balance. Likewise, in the presence of exaggerated parasympathetic tonus a larger dose of atropine is required to block cholinergic function than in the presence of normal autonomic balance.

The assumption that ergotamine merely tends to block adrenergic conduction is misleading. Its primary action on smooth muscle, particularly that which is cholinergically activated, like the gastrointestinal muscle, is to cause contraction.<sup>30</sup> In the intact animal it increases intestinal motility, causes extreme miosis<sup>8,7</sup>, lowers blood sugar<sup>31</sup> and decreases blood pressure.<sup>33</sup> In certain cases the administration of this drug may be followed by increased blood pressure probably due to the contraction of muscular organs. Desensitization of the carotid sinus by ergotamine<sup>18</sup> may be a contributing factor in the rise in blood pressure in these cases. Ergotamine blocks the inhibitory effect of adrenin or sympathetic stimulation on cholinergically activated mechanisms. The inability of adrenin or sympathetic stimulation to block the spontaneous activity or relax the tonus of intestinal muscle in the presence of ergotamine can be explained most satisfactorily on this basis.<sup>9</sup> In the human placenta, which is devoid of nerves but rich in choline<sup>6</sup>, constriction of the blood vessels by adrenin is blocked by ergotoxine.<sup>10</sup> Cholinergic vasodilatation probably is normally inhibited by adrenergic sympathetic stimulation or inhibitory adrenin, resulting in constriction which is synergic with adrenergic constrictor activity. This inhibition of the vasodilators does not take place following the administration of ergotoxine; consequently, the rise is less marked or there may be an actual fall in blood pressure. A similar vasomotor reversal after eserine, which is abolished by atropine, has been demonstrated.<sup>5,17</sup> This also suggests that the inhibitory effects of adrenergic stimulation may be blocked in the presence of sufficient acetylcholine. Linegar et al.<sup>24</sup> have shown that the depressor effect of acetylcholine may be potentiated by ergotamine and that this action may be reversed by atropine. The chief value of ergotamine as an indicator of autonomic function undoubtedly lies in its effec-

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tiveness in testing for the presence of sympathetic inhibitory and adrenin inhibitory effects on cholinergic functions.

The use of atropine to determine the role of cholinergic mechanisms in a given response has become almost routine in physiological experiments. The measurements sought by its use have been mainly of two types: (1) an index of the normal cholinergic activity as indicated by the changes induced when that activity is blocked, and (2) an index of sympathetic function as indicated by the total residual activity following blocking of the cholinergic transmission of nerve impulses in the sympathetic ganglia, the adrenal medulla and the central nervous system. The possible compensatory action of the carotid sinus and other moderator nerves may vitiate both these effects to some extent.<sup>9</sup> Atropine has nevertheless been found useful in the study of autonomic functions, particularly in psychopathic patients<sup>11</sup>, and synergic and antagonistic pharmacologic responses in normal and diseased human subjects.<sup>15,28</sup>

### SIGNIFICANCE OF RESTORATION OF AUTONOMIC FUNCTIONAL BALANCE IN TREATMENT OF ALLERGIC DISEASE

The common association of allergic disease with functional imbalance of the adrenergic and cholinergic autonomic nerves and the evidence that hyperreactivity of the cholinergic nerves is a factor in the etiology of the disease in many cases suggest the importance in the treatment of allergic disease of therapeutic measures designed to restore the autonomic functional balance. The reactions of the adrenergic and cholinergic nerves to the various pharmacologic agents referred to above in the discussion of pharmacodynamic tests of autonomic function also suggest the rationality of the use of sympathetic stimulants and parasympathetic depressants.

The beneficial effect of sympathetic stimulation in the presence of cholinergic hyperactivity is illustrated by the relief obtained in cases of severe asthma by the administration of adrenin or ephedrin. Hyperirritability of the vagus reflex arcs in these cases is indicated by the spastic contractions of the bronchial musculature. The edema of the nasal and bronchial mucous membranes also indicates hyperstimulation of the cholinergic vaso-dilatator nerves in these areas. The relief obtained by the administration of sympathomimetic agents can be explained most satisfactorily on the assumption that the existing cholinergic stimulation has been overcome by adrenergic stimulation of sufficient intensity. The advantage of repeated relaxation of the bronchial musculature by sympathetic stimulation in cases of intractable asthma, according to Barach<sup>2</sup>, may be explained on the assumption that a vicious cycle of bronchial spasm has been overcome by the repeated removal of the stimulation of the muscle receptors during the intervals of relaxation. The increased vascular tonus in the mucous membranes during these intervals also results in decreased capillary permeability, thus limiting the serous output of the glands.

Antibody-allergen reactions obviously are closely related to the specific

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immune reactions. The nervous regulation of the latter is mediated mainly through the cholinergic nerves. Experimental data reported by various investigators, particularly Belak and his collaborators, indicate that the production of immune substances is influenced through both the adrenergic and the cholinergic autonomic nerves. In summarizing the results of investigations begun in 1925, carried out by his collaborators and himself, Belak<sup>4</sup> proposed classification of the immune substances, with respect to their relationships to the autonomic nerves, in two categories: sympathicotropic and parasympathetic. The first category includes the essential nonspecific antibodies, such as the alexins, opsonins, complement, etc., which are always present. Their production is augmented by sympathetic stimulation and inhibited by parasympathetic stimulation. The second category includes the essential specific antibodies, such as antitoxin, precipitin, agglutinin, lysine, etc. The production of these substances is augmented by parasympathetic stimulation and inhibited by sympathetic stimulation.

Other experimental and clinical data which support this point of view are not wanting. In experiments reported by Illenyi and Borzsak<sup>21</sup>, the hemolysin titer was increased by stimulation of the parasympathetic nerves, when the antigen was injected, and decreased by parasympathetic paralysis or stimulation of the sympathetic nerves. The inhibitory effect on hemolysin production of sympathetic stimulation was more marked than that of parasympathetic paralysis. The onset of infectious disease, as indicated by fever, increased metabolism, leukocytosis, etc., is accompanied by sympathetic hypertonus, whereas during the period of recovery, as indicated by the return to normal body temperature, decreased metabolism, disappearance of leukocytosis, increased alkali reserve, etc., parasympathetic tonus gains the ascendancy. At the beginning of an infectious process, therefore, resistance is decreased due to the increased sympathetic tonus which inhibits the production of the specific immune substances, whereas during the later phases resistance is increased due to increased parasympathetic tonus which augments the production of the specific immune substances.<sup>12,19</sup>

The nonspecific immune substances, according to Belak, are related to the emergency functions of the sympathico-adrenal system which responds automatically and promptly to psychic stimulation, pain, muscular exercise, blood pressure, cold and various other changes in the internal and external environments. The relationship of the immediate reactions to infection, intoxication, et cetera, to the sympathico-adrenal system, therefore, is biologically significant. The biological significance of the relationship of the production of specific immune substances to the parasympathetic system is less apparent.

The concept of the regulatory influence of the sympathetic nerves in the production of the nonspecific immune substances and that of the parasympathetic nerves in the production of the specific immune sub-

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stances, as formulated by Belak, undoubtedly expresses a fundamental biologic relationship but cannot be regarded as strictly accurate in the light of our present knowledge of the anatomical distribution of the nerves of sympathetic and those of parasympathetic origin and the role of the neurohumoral mediators. Belak's conclusion that the nonspecific immune substances are related to the emergency functions of the sympathetico-adrenal system is well founded. The specific immune substances undoubtedly are related to cholinergic nerves both of sympathetic and of parasympathetic origin which respond to cholinergic (parasympathetic) stimuli according to a common mode.

Since the antibody involved in any antibody-allergen reaction must be regarded as specific, the nervous regulation of its production, according to Belak's theory, must be mediated through the parasympathetic or cholinergic nerves. Sensitization to a specific allergen undoubtedly involves increased cholinergic stimulation. This further emphasizes the importance of measures designed to restore the functional autonomic balance in the treatment of allergic disease.

The administration of sympathetic stimulants or parasympathetic depressants must be regarded as essentially palliative measures, since their effects usually are of short duration. Complete or permanent restoration of the autonomic balance probably cannot be achieved by these means.

It is significant to point out in this connection that parasympathetic or cholinergic hyperactivity is accompanied by a shift in the acid-base balance toward acidity and adrenergic hyperactivity by a shift in the acid-base balance toward alkalinity. Conversely, changes in the acid-base balance are accompanied by corresponding changes in the autonomic functional balance. The acid-base balance, consequently, plays a significant role in all diseases in which the autonomic nerves are directly involved.

The mechanisms of acid-base balance and water regulation represent the physical and chemical phenomena upon which depend the constancy of the liquid environment of the tissue cells which limits within a narrow range the variations in osmotic pressure, chemical reaction, fluid volume, ionic concentration, etc. The ions involved are mainly those of the electrolytes sodium, potassium and calcium. Potassium constitutes the intracellular base; sodium, the base of the extracellular fluids. Calcium is essentially acid. Sodium, potassium and calcium are neutralized or counterbalanced in their physiological ratios by the physical action of one ion upon another regardless of which salts of these electrolytes are present.

The body fluids normally are slightly alkaline. Actual acidity of these fluids, as is well known, is incompatible with life. Acidosis, as this term is commonly used, implies only decreased alkalinity. Since the total quantity of acid radicals derived from an ordinary diet greatly exceeds the intake of fixed base, conservation of base is highly important and depends largely on the functional state of the kidneys. Regulation of the water balance depends on the retention of electrolytes, particularly sodium, in appropriate

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concentration. This is accomplished either by the conservation of base or by the excretion by the kidneys of excess base.

The results of clinical studies reported by Hollo and Weis<sup>20</sup> have demonstrated that calcium chloride administered intravenously in therapeutic doses reduces the bicarbonate content of the blood plasma but increases the H-ion concentration of the blood and the alveolar carbon dioxide tension in the lungs. The bicarbonate content of the blood plasma also is reduced by the administration of calcium chloride and calcium lactate by mouth. The results of animal experiments reported by Fürst<sup>13</sup> and others also show that the acid-base balance is shifted toward acidity by the administration of calcium and that an increase in the potassium-ion concentration results in a shift in the acid-base balance toward alkalinity. According to Reid<sup>20</sup> the acid-base balance in the blood plasma may be restored by the intravenous administration of sodium chloride regardless of whether the imbalance represents a shift toward alkalinity or toward acidity.

These data suggest the possibility of restoration of the acid-base balance in allergic patients by simpler measures, such as ordinary alkali therapy and appropriate diet, adapted to the requirements of every individual patient on the basis of a study of his or her physiological reactions. In cases with marked emotional factors appropriate psychotherapy is indicated, since the emotional states which tend to precipitate allergic reactions commonly are accompanied by a shift in the acid-base balance toward acidity. In peptic ulcer patients and many normal subjects, according to Mittelmann and Wolff<sup>27</sup>, gastric acidity is increased during periods of experimentally induced anxiety, hostility and resentment, whereas pre-existing hyperacidity is decreased during periods of induced feelings of contentment and well-being.

Changes in the autonomic functional balance associated with induced changes in the acid-base balance have been amply demonstrated; consequently, restoration of the autonomic balance by appropriate therapeutic measures designed to restore the acid-base balance should not be regarded as beyond the range of possibility in many cases of allergic disease. Treatment directed toward the autonomic nerves primarily, if it results in restoration of the autonomic functional balance, will also affect the acid-base balance favorably. In cases with obvious emotional factors, appropriate psychotherapy, with or without reference to the acid-base balance, should be regarded as a useful adjunct to other therapeutic measures.

### BIBLIOGRAPHY

1. Abramson, H. A.: Physical and psychic allergy. *J.A.M.A.*, 118:229, 1942.
2. Barach, J. H.: Ketosis in health and disease. *Am. J. Digest. Dis.*, 10:134-138, 1943.
3. Bender, M. B.: The reaction of the smooth muscle of the denervated iris in anaphylaxis. *J. Immunol.*, 47:483-491, 1943.
4. Belak, S.: Schützstoffbildung als vegetative Funktion. *Klin. Wchnschr.*, 18: 472-474, 1939.

## AUTONOMIC NERVOUS SYSTEM—KUNTZ

5. Bülbbring, E., and Burn, J. H.: The sympathetic dilator fibers in the muscles of the cat and dog. *J. Physiol.*, 83:483-501, 1935.
6. Chang, H. C., and Gaddum, J. H.: Choline esterase in tissue extracts. *J. Physiol.*, 79:255-285, 1933.
7. Crouch, R. L., and Thompson, J. K.: Autonomic functions of the cerebral cortex. *J. Nerv. & Ment. Dis.*, 89:328-374, 1939.
8. Dale, H. H.: On some physiological actions of ergot. *J. Physiol.*, 34:163-206, 1906.
9. Darrow, C. W.: Physiological and clinical tests of autonomic function and autonomic balance. *Physiol. Rev.*, 23:1-36, 1943.
10. Euler, U. S.: Central depressor action of adrenaline and its inhibition by ergotoxine. *J. Physiol.*, 92:111-123, 1938.
11. Fentress, T. L., and Solomon, A. P.: Galvanic skin reflex and Danielopol test in psychoneurotic patients. *Arch. Neurol. and Psychiat.*, 35:770-775, 1936.
12. Frei, W.: Allgemeine pathologische Physiologie des vegetativen Nervensystems bei Infektionskrankheiten und Immunitätsvorgängen. *Erg. Allg. Pathol. u. path. Anat. I. Mensch. u. Tiere*, 34:181-225, 1939.
13. Furst, T.: Ziffernmässige Unterschiede bei der praktischen Verwendung von Konstitutionsindizes bei Schulkinderuntersuchungen. *Münchener med. Wochenschr.*, 72:1073-1074, 1925.
14. Gillispie, R. D.: Physiological factors in asthma. *Brit. M. Jr.*, 1:1285, 1936.
15. Grosse-Brockhoff, F., and Kalender, F.: Über die Antagonismus von Sympatheticus und Vagus unter der Einwirkung adrenalinähnlicher Substanzen. *Arch. f. exper. Path. u. Pharmakol.*, 188:383-399, 1938.
16. Heim, F.: Allergie und vegetatives Nervensystem. *Arch. f. exp. Path.*, 196:51-86, 1940.
17. Herwick, R. P., and Linegar, C. R., and Koppanyi, T.: Effect of anesthesia on vasomotor reversal. *J. Pharmacol. & Exper. Therap.*, 65:185-190, 1939.
18. Heymans, C., Bouckaert, J. J., and Dautrebande, L.: Sinus carotidien et reflexes respiratoires; influences respiratoires reflexes et l'acidose, de l'acolose, de l'anhydride carbonique, et l'ion hydrogène et de l'anokémie. Sinus carotidiens et échanges respiratoires dans les poumons et au delà des poumons. *Arch. internat. de pharmacodynamie et de thérapie*, 39:400-449, 1930.
19. Hoff, F.: Infektionsabwehr und vegetatives Nervensystem. *Deutsch. med. Wochenschr.*, 67:417-420, 1942.
20. Hollo, J., Weis, S., and Csepai, K.: Influence of blood reaction and blood sugar on epinephrin reaction. *Wien. Arch. f. inn. Med.*, 10:213-222, 1925.
21. Illenyi, A., and Borzsak, L.: Der Einfluss des vegetativen Tonus auf die Bildung des Hemolysins. *Ztschr. f. Immunitt. u. exp. Ther.*, 9479-82, 1938.
22. Jacobs, J. L., Kelley, J. J., and Sommers, S. C.: Hereditary predisposition to sensitization in guinea pigs. *Proc. Soc. Expt. Biol. & Med.*, 48:639-641, 1941.
23. Landsteiner, K., and Chase, M. W.: Breeding experiments in reference to drug allergy in animals. *Proc. Int. Cong. Microbiol.*, 772, 1940.
24. Linegar, C. R., Herwick, R. P., and Koppanyi, T.: Studies on synergism and antagonism of drugs; further studies on action of nicotine and physostigmine on sympathetic ganglia. *J. Pharmacol. & Exper. Therap.*, 65:191-204, 1939.
25. Lortat-Jacob, E.: Le Sénit de tolérance cutanée eczéma, rôle du sympathique. *Paris Med.*, 104:447, 1937.
26. Milian, G.: Nature de l'eczéma. *Rev. franc. Derm. Venereol.*, 12:388, 1936.
27. Mittelmann, B., and Wolff, H. G.: Emotions and gastroduodenal function; experimental studies on patients with gastritis, duodenitis and peptic ulcer. *Psychosom. Med.*, 4:5-61, 1942.
28. Myerson, A., Loman, J., and Dameshek, W.: Physiological effects of acetyl-beta-methylcholine (mecholyl) and its relationship to other drugs affecting the autonomic nervous system. *Am. J. M. Sc.*, 193:198-213.
29. Reid, L. E.: The mechanisms of acid-base balance and water regulation. *Am. Res. in Anesth. & Analg.*, 20:301-313, 1941.
30. Rothlin, E.: Zur Pharmakologie der Mutterkornalkaloide. *Arch. f. exper. Path. u. Pharmakol.*, 138:115-119, 1929.
31. Shpiner, L. B.: Effect of ergotamine on blood sugar level. *Am. J. Physiol.*, 88:245-250, 1929.
32. Wenger, M. A.: The measurement of individual differences in autonomic balance. *Psychosom. Med.*, 3:427-434, 1941.
33. Wright, S.: Studies of reflex activity in involuntary nervous system. II. Action of ergotamine on vasomotor reflexes. *J. Physiol.*, 69:331-347, 1930.

## DERMATOLOGIC MANIFESTATIONS OF FAMILIAL NONREAGINIC ALLERGY

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**I**N previous communications on the general topic of familial nonreaginic allergy a few cases were described in which there were cutaneous lesions, which were found to be entirely controllable through mere avoidance of the allergens that caused specific tachycardia. My experiences have now included a sufficient number of such instances, perhaps, to warrant separate consideration of the group.

Today's presentation is not intended as finished proof of the importance of nonreaginic allergy as a cause of the several cutaneous manifestations that I shall mention. My selection of this topic was primarily a device or excuse for again directing your attention to the constant cardiac reaction which I have found to be so dependable a criterion of the nonreaginic allergic effect. I hoped also to arouse the interest of some of you in the possible applicability of that criterion to the specific diagnosis and relief of some cutaneous manifestations of allergy.

My experiences have impressed me with a fact that is already known to those dermatologists who are particularly interested in dermatologic allergy, namely, that the skin is *variously* affected by allergic disease. There are, indeed, some dermatologists who are convinced that the list of recognized cutaneous allergic manifestations will increase with further knowledge.

### CUTANEOUS CIRCULATION

A phenomenon of general significance that is sometimes apparent to the unaided eye is the favorable change in some patients in the arteriocapillary circulation after avoidance of all the pulse-accelerating allergens.

Previous to treatment the skin and nails may be pale and variously sallow, depending upon the pigmentation, and the nails may show a tendency to become wavy and cracked. The base of the nail may become loose, exposing the raw, bleeding surface of the nail-bed. The lips and the back of the hands may become chapped in winter and the thick skin of the fingertips at the sides of the nails may become cracked and bleeding.

That a deficient circulation is the chief cause of these latter lesions is evidenced by the fact that those of the hands can be in large part prevented or greatly improved if the patient merely keeps the hands quite warm at night by wearing soft and sufficiently thick cotton gloves in bed.

After successful treatment of the food-allergy the skin and nails become

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pink, the nails are no longer cracked, and the tendency of the skin to chap and to crack at the finger-tips disappears.

In one case (A.F.C.) the feet, previous to treatment, were constantly cold in winter and were slightly frost-bitten on one occasion. After treatment the feet have never been cold in winter, even when exposed to the lowest temperatures in the usual footwear (cotton socks).

#### SECRETORY ACTIVITY OF THE SEBACEOUS GLANDS

Some patients with familial nonreaginic allergy exhibit a constantly excessive secretory activity of the sebaceous glands, often associated with the development of comedones. In two patients this condition existed in a marked degree previous to treatment. Patient J. V., whose chief complaints were continual headaches, mild bronchial asthma and physical tiredness, characterized the condition of his nose with the expression "a grease-ball."

After successful dietary treatment the patient was relieved of all of his allergic symptoms, and the excessive activity of the sebaceous glands ceased.

In the second patient, also, the improvement in this respect was remarkable and permanent.

#### CHRONIC URTICARIA

It is common knowledge that chronic urticaria may be due to the eating of certain foods. Naturally, the culprit food has been easily identified only when it was the only excitant and if it was *not too frequently eaten*. Naturally, too, the foods that were so identified have been thought to possess some special urticariogenic property, and they are actually so listed by some writers, who advise avoidance of all of them by sufferers from chronic urticaria.

Study of the five cases, presently to be described, with the criterion of specific acceleration of the pulse has revealed the following tentative conclusions:

1. Chronic urticaria is at least frequently a symptom of familial nonreaginic allergy.
2. While it seems unlikely that any allergenic food will be found never to be urticariogenic, it seems to be a fact that among the list of an affected person's identified food allergens, some foods always or frequently cause urticaria, whereas others do so much less frequently, if at all.
3. Severe urticaria in some affected persons *seems* to be caused by inhaled allergen ("bed dust" in one of the cases described). However, this has not been proved.

*Case 1.*—January, 1940. J. G., male, aged thirty-six. Symptoms: incapacitating three-day headaches at one- to two-week intervals, frequent urticaria and angio-neurotic edema, and heartburn. All of these symptoms ceased completely and

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TABLE I. PULSE-DIET RECORD

Case 3.—C. G., aged fifteen

1944	Jan. 12	13	14	15	16	17	18
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
B.R.—	56	55	51	50	52	54	53
Br.—	67	72	78	60	60	62	64
30 m	79	84	76	58	63	63	66
60 m	77	88	72	58	62	63	65
90 m	78	88	72	57	63	63	68
Diet—							
Shredded <b>Wheat</b> , sugar milk	toast milk	rice (boiled) salt	rice (boiled) salt	rice, butter egg, milk baked apple	rice, egg baked apple sugar milk	egg, rice baked apple sugar milk	
Mid A.M.							
30 m	88	65	59	65	62		
60 m	72	72	61	65	63		
90 m	64	70	60	64	64		
Diet—	apple	apple	apple	carrot	carrot		
Lunch—							
30 m	75	68	78	68	60	63	68
60 m	74	68	70	74	84	64	65
90 m	74	68	68	58	74	65	67
Diet—							
liverwurst milk, <b>bread</b> orange ginger-cookies	chicken, milk lettuce orange <b>bread</b>	2 eggs (boiled)	eggs (boiled)	veal rice milk baked apple	egg milk baked apple	egg milk baked apple	
Mid P.M.							
30 m	75	72	64	60	63		68
60 m	75	76	74	60	62		66
90 m	72	68	60	60	62		66
Diet—nothing	milk	milk	milk	baked apple milk		lettuce celery	
Dinner—							
30 m	74	74	64	60	63	65	68
60 m	69	85	61	62	64	65	70
90 m	65	78	63	63	64	64	69
Diet—chicken rice, milk cornstarch celery, carrot, lettuce	nothing	chicken	chicken, rice butter baked apple sugar, cream	chicken, rice butter baked apple milk, sugar	chicken potato milk baked apple	ham, potato carrot milk baked apple	
Ret.—	65	72	58	60	63	66	64
hives today				hives less	no hives after lunch	no hives wt. 129	no hives wt. 128

permanently after wheat, cane sugar and coffee had been entirely eliminated from the diet.

Headache, accompanied with tachycardia up to 110 but with *no urticaria* nor heartburn, was induced by wheat eaten in quantity at the three meals of the test on one day. Heartburn without headache or urticaria and with a moderate tachycardia (90) followed a single ingestion of cane sugar (two tests).

Urticaria and angioneurotic edema with delayed headache and no heartburn followed the ingestion of coffee. There was only slight tachycardia (80); normal maximum 74.

Other cereals (rice and rye) caused no symptoms and only a slight tachycardia (80).

*Case 2.*—May, 1940. Mrs. A. P., aged seventy. Symptoms: marked chronic generalized *urticaria* ("dollar-size"), chronic cough, constipation, "heart attacks," fainting, weakness, tiredness, and occasional headaches. All of these symptoms ceased completely and permanently after the following foods had been entirely eliminated from the diet: beef, cow's milk, egg, corn, orange, olive, banana, yeast, proprietary laxative. The normal pulse range was found to be 70 to 74.

Urticular attacks, accompanied with tachycardia up to 100, were induced sep-

## FAMILIAL NONREAGINIC ALLERGY—COCA

TABLE I. PULSE-DIET RECORD (Cont'd)

Jan. 19	20	21	22	23	24	25
Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
B.R.— Br.— 30 m 60 m 90 m Diet—banana egg, rice milk sugar	53 65 67 66 67 orange egg rice milk	52 63 64 63 65 grapefruit egg rice milk	53 62 64 63 65 no breakfast	52 — — — — Ry-Krisp banana milk	52 59 60 59 59 pineapple Ry-Krisp milk	52 59 60 58 59 pineapple Ry-Krisp milk
Mid. A.M.— 30 m 60 m 90 m Diet—dates	68 63 60 63 dates	64 62 64 63 dates	63 65 64 62 tomato	60 58 59 58 chocolate bar	58 59 60 59 banana	60 58 59 57 raisins
Lunch— 30 m 60 m 90 m Diet—egg milk baked apple sugar	62 63 64 65 egg milk lettuce baked apple	64 65 63 64 egg milk baked apple	61 60 62 61 ham broccoli baked apple milk	60 61 59 60 lamb chop potato, carrot broccoli, let- tuce, celery orange, apple milk	59 60 61 59 egg pineapple lettuce milk	60 58 59 58 lamb chop lettuce milk orange
Mid P.M.— 30 m 60 m 90 m Diet—orange	64 66 64 60 prunes	64 66 63 65 prunes peanut-butter	60 63 60 62 prunes peanut-butter	59 62 61 59 tomato juice sugar	60 57 56 58 chocolate bar	58 59 60 58 raisins
Dinner— 30 m 60 m 90 m Diet— ham, potato carrot, milk baked apple	62 67 65 62 ham, potato carrot str. bean baked apple	64 61 60 62 fish potato, car- rot, peas baked apple	61 62 60 62 lamb chop potato, flets orange, banana celery, milk	59 58 59 58 Ry-Krisp peanut-butter milk	58 59 57 58 lamb, potato onion, carrot lettuce, par- sley, celery pineapple, date orange, Ry- Krisp	59 61 66 60 fish, potato onion, tomato broccoli, celery Strawberry milk
Ret.— wt. 128	61	sore throat wt. 127	sore throat wt. 128	sore throat Tt. 127	sore throat "feeling sick all day"	throat healed "feels well" wt. 127
					wt. 126	—

arately by the following foods: beef, orange, banana, olive, egg, laxative, yeast, corn. All other cereals and cane sugar were tolerated without causing any tachycardia or other symptoms.

It is noteworthy that on the first day of the trial diet, exhibiting "large hives and a bad cough" on rising, the patient suffered no further urticaria, although she ate nothing on that day but beef, which caused an almost constant tachycardia reaching a maximum of 100, and which, some weeks later, at a single test, caused a severe urticarial attack. This again illustrates the depressing effect of continued allergic insults upon the reactive mechanism of a shock tissue. Not all the shock tissues are necessarily depressed at one time; this is seen in the fact that on that day there were, beside the tachycardia, "some coughing and dull headache."

*Case 3.*—January, 1944. C. G., female, aged fifteen. Symptoms: chronic urticaria, recurrent headaches, physical tiredness, occasional dizziness, and canker sores. The patient became symptom-free after the range of her pulse had been brought to her normal limits (52 to 61) through avoidance of her three food allergens—

## FAMILIAL NONREAGINIC ALLERGY—COCA

TABLE I. PULSE-DIET RECORD (Cont'd)

Jan. 26	27	28	29	30	31	Feb. 1
Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
B.R.— 52	52	52	52	54	53	52
Br.— 58	57	50	50	65	60	60
30 m 60	58	58	90	63	58	58
60 m 67	59	57	86	62	60	59
90 m 61	57	58	86	62	59	60
Diet—						
strawberries	peaches	cranberry	toast (wheat)	rice	Ry-Krisp	grapefruit
Ry-Krisp	cranberry	rice	peanut-butter	milk	applesauce	oatmeal
milk	rice	milk	apple	orange	milk	milk
		sugar	milk		sugar	sugar
Mid A.M.—						
30 m				61		
60 m				58		
90 m				58		
Diet—				59		
Lunch— 61	58	58	86	59	60	60
30 m 60	60	60	86	61	59	61
60 m 59	59	59	87	60	61	59
90 m 58	57	59	84	61	60	59
Diet—						
egg, lettuce	chicken	egg	lamb chop	pork	chicken	ham
celery, milk	carrot	celery	carrot, lettuce	potato	carrot, let-	carrot
buttered	lettuce, milk	lettuce	milk	str. bean	tuce, celery,	milk
	orange	milk			orange, milk	orange
			"covered with			
			hives; face			
			swollen."			
Mid P.M. 57	57					
30 m 58	58				60	60
60 m 58	57				59	59
90 m 57	58				58	58
Diet—orange	orange				59	60
					raisins	apple
Dinner— 58	59	59	78	60		
30 m 59	60	60	76	59		
60 m 58	61	58	76	61		
90 m 58	60	58	74	59		
Diet—chicken	squash, potato	fish, squash	chicken, egg	Ry-Krisp	ham	corn, spinach
peas	lamb, lettuce	tomato, onion	rice, potato	milk, peanut-	asparagus	pork, potato
rice	Ry-Krisp	celery, milk	celery	butter	tu4rip, rice	oatmeal, egg
milk	peanut-butter	buttered	lemon	applesauce	milk	sugar, lemon
			milk	rice-pudding		juice
Ret.— 57	58	59	68			
wt. 126	wt. 126	wt. 126	wt. 126	wt. 126	59	—
					few hives	no hives
						(head cold)

wheat, beef and strawberry. Other cereals and raspberry cause no tachycardia and no other symptoms.

Table I shows the daily pulse-diet record of C. G. for the first three weeks.

The slowing of the pulse after the evening meal on January 12 suggested that no allergenic food had been eaten at that meal. Hence, the marked tachycardia occurring after breakfast the following day was not attributed to milk but to the wheat (toast), which had not been eaten on the previous evening but which had been eaten on the previous morning, when also there was a subsequent moderate tachycardia.

Wheat was last eaten at noon on the 13th when the cardiac shock-tissue was in depression from the morning reaction. However, there was a marked, delayed effect in the evening (85), which continued in lessening degree through the next three days until it was overpowered by a fresh reaction caused by the eating of veal.

The urticaria which was present at the beginning of the dietary examination persisted into the third day.

The tachycardial reaction to veal continued into the sixth day (62 on January 22), yet there was no urticaria at any time in that period, nor any other symptom.

## FAMILIAL NONREAGINIC ALLERGY—COCA

In the following two days and in the third day until the evening meal (strawberry), the pulse-rate did not exceed the normal maximum (61).

Strawberry in two tests caused only a very slight tachycardia and no urticaria nor other symptom.

After another two days (January 27, 28) in which the pulse-range remained normal, a final test of wheat was made, resulting in a marked tachycardia, which lasted only twenty-four hours. The accompanying urticaria and angioneurotic edema continued for another day.

The tachycardia occurring after dinner on February 1 was believed to be an effect of the brief attack of common cold. The patient is not sensitive to corn.

There was a loss of four pounds in weight in less than four weeks—probably fluid.

The etiological study of chronic urticaria is complicated by the occasional instances of spontaneous recovery, or of a lessening of the severity of the condition. This occurrence prevented a definite conclusion as to the cause of the urticaria in the fourth case.

*Case 4.*—A. McC., female, aged thirty-two. First consultation, May, 1943. The patient exhibited nine of the most common symptoms of food allergy but complained chiefly of chronic urticaria, which was severe only in the night, regularly preventing sleep after midnight. The pulse was erratic, ranging from 60 to 83, but the rates above the estimated normal maximum of 74 could not be ascribed to any item of diet. This fact and the constant recurrence of the nocturnal attacks suggested an environmental allergen, possibly bed dust or feathers.

Dust-proof covers were applied to bed mattress and pillows in June, 1943, and the nocturnal attacks immediately ceased. Thereafter, only occasional wheals appeared in the daytime and dermographism persisted.

In March, 1944, the dust-proof covers were removed, but thereafter there has been no recurrence of the nocturnal attacks, although one or two wheals still appear in the evening as before. The pulse is still erratic.

### *Additional Note*

Still not being satisfied with the improvement noted in the foregoing, the patient decided to undergo the conservative sympathectomy performed by Dr. Max Danzis and described in an earlier report.<sup>1</sup> The operation was done on June 27, 1944, and healing of the wound was rapid and uneventful. There was some pain in the thigh (inner aspect) on the side of the operation, which gradually disappeared.

There were a few hives on the day of the operation but none whatever at any time since.

The pulse, which before the operation had ranged erratically between 65 and 84, now shows a normal range of 65 to 76 on a large dietary list. After an evening meal containing onion and parsley (offender not yet further identified), the pulse-rate reached 80 with carry-over effect to the same point on the next morning.

*Case 5.*—Mrs. S. W. C., 1942, aged forty-seven. Symptoms: chronic urticaria (for one year), migraine, constipation. B. P. 128/76. Pulse range before treatment 66 to 100. Normal range, 56 to 66. Pulse-accelerating allergens: egg, citrus fruit, cereals, cane sugar, banana, plum family, fish, beef, lamb.

After avoidance of these foods the severity of the urticarial attacks was decidedly lessened but they did not cease, and the pulse record shows the effect of some extradietary allergen, probably environmental. The patient was so much better that she would not take the trouble to try to identify this allergen. She reports recently that she no longer restricts her diet and her urticaria is relatively negligible.

## FAMILIAL NONREAGINIC ALLERGY—COCA

TABLE II. PULSE-DIET RECORD  
Case 5. Mrs. S. W. C., aged forty-seven

1942		Feb. 2	3	21	28	Mar. 1	3	9
		Pulse	Pulse (hives)	Pulse (few hives)	Pulse	Pulse	Pulse	Pulse (hives)
B.R.—	67		78	62	58	56	60	58
Br.—	70		80	68	66	72	74	64
30 m	78		98	68	68	74	72	64
60 m	82		86	66	66	74	80	64
90 m	84		87	60	66	84	72	64
Diet—								
corn flakes		2 eggs	(more hives)	bacon milk coffee	bacon milk coffee	bacon milk	bacon milk (hives)	milk
sugar								
Mid.								
A.M.—	82		78					
30 m	72		90					
60 m	76		96					
90 m	82		82					
Diet—milk (headache)		grapefruit (recurrence of hives)						
Lunch—								
30 m	74		84	60	66	60	66	64
60 m	88		74	60	66	60	74	64
vomited	—		74	68	66	64	74	64
90 m	66							
Diet—lamb		pork	—	62	66	64	70	64
peas		carrot		peas carrot Lima beans	beets celery cheese tea	ham, tomato str. beans celery grapes coffee (hives)	chicken peas spinach	chicken str. beans carrot
Mid. P.M.								
30 m			84		62			
60 m			90		68			
90 m			88		66			
Diet—		banana (hives)			—			"hives today"
					chocolate peppermint (hives)			
Dinner—	—		80	64	64	58	68	64
30 m	—		84	64	64	60	68	64
60 m	—		80	66	64	62	66	64
90 m	—		78	66	64	62	66	64
Diet—(aspirin)		chicken str. bean		chicken potato str. bean Vi. B. Com- plex (few hives)	chicken, tomato, carrot grapes Vi. B. (few hives)	chicken ham milk	ham carrot potato celery (hives in night)	chicken potato peas coffee
Ret.—	84		78	—	—	—	—	
1st day, test								

### ATOPIC DERMATITIS

The pulse-controlled dietary method has been applied in a few cases of atopic dermatitis with inconclusive but, on the whole, encouraging results.

### SUMMARY

Observations are reported indicating that familial nonreaginic food allergy may cause:

(1) Significant disturbance of the general peripheral circulation (pallor, "chapped" skin, tendency to chilblain or frostbite); (2) abnormalities of the nail; (3) excessive secretion of the sebaceous glands of the skin; and is a frequent cause of (4) chronic urticaria.

## FAMILIAL NONREAGINIC ALLERGY—COCA

### REFERENCE

1. Coca, A. F.: Sympathectomy as an aid in the relief of familial nonreaginic food allergy. *Ann. Allergy*, 2:213-224, (May-June) 1944.

### DISCUSSION

DR. LESTER REDDIN (Pearl River, N. Y.): Although the symptoms that I have exhibited, that is, at least prior to September, 1940, are not dermatologic, merely as a matter of interest, Doctor Coca thought it might be well to mention the non-dermatologic symptoms which I have experienced.

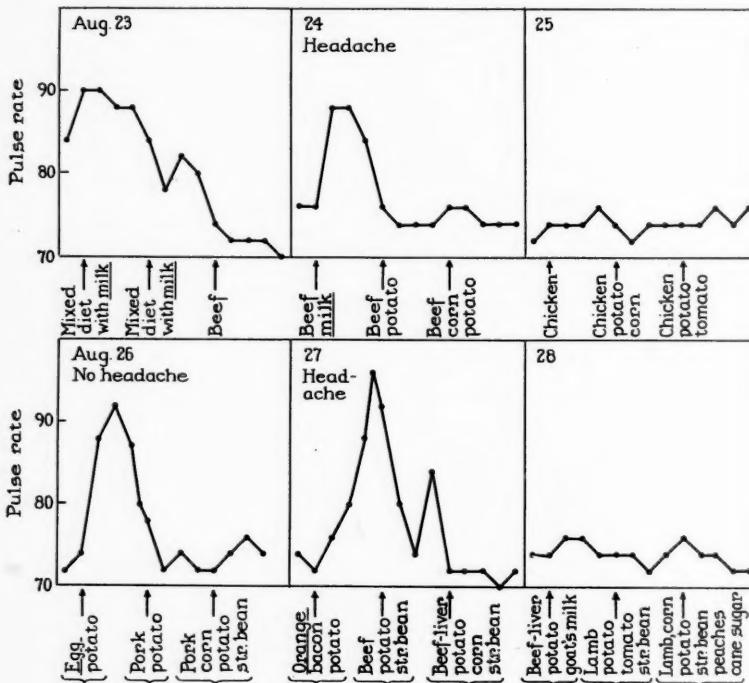


Fig. 1.

Prior to 1940, that is, September 1940, I had been suffering for some years with chronic sinusitis, dizziness on occasions, migraine and tachycardia, which, while I was in college, prompted the cardiologist there at the health service of the university to keep me under observation for several months. In the summer of 1940 I was experiencing quite a bit of difficulty with rhinitis in the evenings especially, and inasmuch as I worked with animals, my family physician suggested that I see Doctor Coca and have certain skin tests done for danders.

All of the skin tests for danders as well as for foods were negative. There was no local reaction to any of them. We then followed out the trial diet, taking the pulse record for two days with the general diet which I had been following, getting the range of pulse which I had experienced with that general diet. Then we limited the diet to beef and established the normal pulse rate. From then on, every day after

## FAMILIAL NONREAGINIC ALLERGY—COCA

the pulse again returned to normal following an attack from an excitant, a new food was added.

On the first day when the mixed diet was fed, including cow's milk, the pulse range was up to 90 (Fig. 1). That evening the diet was limited entirely to beef, and a normal pulse rate was established. The second morning beef and milk were again eaten, and the pulse ran up close to 90. After it returned to normal, potatoes were added, with no apparent increase in the pulse rate, and that evening another food was added—corn. On the day of the 25th the pulse remained within what has now been established as the normal limit for myself, the variations being anywhere from 70 to 76. Regardless of the time of day or the digestive activity, that pulse remains very constantly in those limits.

You can also see that following the milk, there was very severe migraine. For breakfast the morning of the 26th eggs were added and again a tachycardia persisted, although no headache or any other symptoms were shown. Throughout this entire time the rhinitis, or rather the chronic sinusitis had been continuing. There was no improvement of that during the test. The next food to be added which caused a very prompt rise in the pulse rate was orange, which also caused a mild migraine. Various other foods were added from time to time throughout the few days that I was under examination, with no effect whatsoever. So that in the whole course of the examination, which was around four days, a very short case, I had eliminated all of the foods from the diet which were allergenic.

The sinusitis prior to the trial diet had been treated by the various methods without surgery as well as culturing and staphylococcal therapy. None of the means of therapy gave me lasting results. Following the trial diet there was not very much improvement by avoiding the allergic foods, but toxoid therapy was again resumed, and this in conjunction with avoidance of the allergic foods gave complete recovery within about two months, so that sinus plates taken in January showed absolutely no signs of any inflammation of the sinuses. The plates were taken at our local hospital.

Although I am not as good as some of Doctor Coca's other patients, I avoid the allergenic foods pretty well. There are occasions when I dissipate and suffer somewhat from that dissipation. There were no skin lesions at all throughout the whole study, so, unfortunately, I am not talking on this subject today, but that is the picture as I have seen it and as Doctor Coca has interpreted it from my pulse rate.

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*Frequency of Allergy in Orthodontic Patients.* Straub, W. J.: Eye, Ear, Nose & Throat Monthly, No. 31, 1944.

The author reviews the literature as it is applied to the production of abnormal facies, growth and development in allergic children. In the present study, 104 patients of the orthodontic division (fifty-eight female and forty-six male) were completely investigated from the allergic standpoint. Forty-one (39.4 per cent) were definitely allergic, thirteen (12.5 per cent) were borderline and fifty (48.1 per cent) were negative upon the basis of history and skin tests. Various other medical conditions (allergic and nonallergic) were distributed among these patients. Blood studies showed eosinophilia in seventy-four patients. Of the forty-one patients with chronic nasal allergy, twenty-four (61.5 per cent) had contracted maxillary arches with accompanying protraction of the anterior teeth and retraction of the mandible or mandibular teeth. This high percentage suggests that in most cases of nasal blockage, associated with facial deformities, allergy must be suspected and considered definitely related to the development of dento-facial anomalies. Bibliography. L. J. H.

## AGGLUTINATION OF POLLEN-ANTIGEN-COATED BACTERIA BY SERA OF RAGWEED-SENSITIVE PATIENTS

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**A**N unusual method was used to study agglutinins in the sera of known ragweed-sensitive patients. It was demonstrated by Jones<sup>1</sup> that antigenic properties can be transferred. Thus, bacteria, after being coated by a test antigen, were agglutinated by an immune serum corresponding to that antigen. For example, Roberts and Jones<sup>2</sup> adsorbed a specific antigen, horse serum, upon bacteria which were subsequently agglutinated in the presence of a specific antibody, anti-horse serum, even in high dilutions. An attempt was therefore made to transfer the antigenic properties of ragweed pollen, or its extract, upon *Serratia marcescens* (*Bacterium prodigiosum*) and to test against the treated bacteria the sera from ragweed-sensitive patients.

*Serratia marcescens* was chosen as a recipient of the antigenic properties of ragweed pollen because (1) it is non-pathogenic; (2) its presence in suspension is easily demonstrable; (3) its agglutination may be easily visible macroscopically; (4) a specific antibody for it, as a rule, has not been found in human sera. Twenty-four-hour-old cultures (grown at room temperature to obtain red colonies) were used throughout the experiment. The antigens used were giant and dwarf ragweed pollens.

The sera for controls were obtained from volunteers known to be non-allergic and on whom intracutaneous tests to ragweed pollen extract were negative.

In order to determine the optimum conditions for transference of antigenic properties upon the bacteria, the following bacterial preparations were made:

1. One gram of ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water.
2. One gram of ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water heated to 60° C. for five minutes.
3. One gram of ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water phenolized to 0.4 percent.
4. One gram of etherized ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water.
5. One gram of etherized ragweed pollen was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water heated to 60° C. for five minutes.

From the Department of Laboratories and the Department of Allergy, Israel Zion Hospital, Brooklyn, N. Y.

#### AGGLUTINATION—ALPERSTEIN

6. One gram of ragweed pollen washed in 10 per cent formalin was added to a 10 c.c. suspension of *Bacterium prodigiosum* in sterile distilled water.

7. One gram of ragweed pollen washed in 10 per cent formalin was added to 10 c.c. of a suspension of *Bacterium prodigiosum* in sterile distilled water heated to 60° C for five minutes.

8. *Bacterium prodigiosum* was suspended in 10 c.c. of a 1:100 dilution of ragweed extract (a 50 per cent glycerinated Coca's solution with 0.4 per cent phenol).

9. *Bacterium prodigiosum* was suspended in 10 c.c. of a 1:100 dilution of ragweed extract in Coca's solution.

10. *Bacterium prodigiosum* was suspended in 10 c.c. of a 1:100 dilution of a saline extract of ragweed pollen.

All suspensions of bacteria and ragweed antigen were allowed contact for twenty-four hours in an incubator at 37° C. and were subsequently placed in a refrigerator until ready for use. All bacterial suspensions with pollen antigen were then centrifuged to separate the pollen from the bacteria. The bacteria were washed with sterile normal saline solution, and then resuspended in sterile normal saline solution just before tests were made. The opacity of approximately one billion organisms per cubic centimeter was used as a standard. Microscopic examination of each bacterial suspension was made to rule out the presence of pollen granules or clumping of bacteria.

The tests were performed as follows:

1. Test tubes with 1 c.c. of serum from ragweed-sensitive patients were arranged in serial dilutions in racks (in sterile normal saline solution) of 1:10, 1:20, 1:40, 1:80, 1:160, 1:320.

2. Test tubes with 1 c.c. of serum from non-allergic patients were similarly arranged in serial dilutions.

3. One c.c. of a pollen-antigen-coated bacterial suspension was added to each test tube of the series of dilutions as made above.

4. Thorough mixing was obtained by shaking the racks for a few minutes.

5. All racks with the test tubes were placed in an incubator at 37°C for two hours and a preliminary reading was made.

6. All racks were then placed in the refrigerator over night. The next morning, they were removed and allowed to stand at room temperature for one hour before final readings were made.

7. Readings were done macroscopically as well as microscopically. Agglutination of *Bacterium prodigiosum* is easily read macroscopically.

The results were:

1. No agglutination of any of the pollen-antigen-coated bacterial suspensions was observed with any of the ten control sera (from the non-allergic patients).

## AGGLUTINATION—ALPERSTEIN

2. With the sera of known ragweed-sensitive patients agglutination was observed in the following pollen-antigen-coated bacterial suspensions listed above as:

- No. 1— 2 sera in dilutions up to 1:20  
24 sera in dilutions up to 1:40  
3 sera in dilutions up to 1:80
- No. 2— 2 sera in dilutions up to 1:20  
24 sera in dilutions up to 1:40  
3 sera in dilutions up to 1:80
- No. 4— 1 serum in dilution up to 1:20  
24 sera in dilutions up to 1:40  
4 sera in dilutions up to 1:80
- No. 5— 1 serum in dilutions up to 1:20  
24 sera in dilutions up to 1:40  
4 sera in dilutions up to 1:80
- No. 6—11 sera in dilutions up to 1:20  
16 sera in dilutions up to 1:40  
2 sera in dilutions up to 1:80
- No. 7—11 sera in dilutions up to 1:20  
16 sera in dilutions up to 1:40  
2 sera in dilutions up to 1:80
- No. 9— 3 sera in dilutions up to 1:20  
23 sera in dilutions up to 1:40  
3 sera in dilutions up to 1:80

3. No agglutination was observed in pollen-antigen-coated bacterial suspensions listed as No. 3, No. 8, and No. 10 with any of the sera of the known ragweed-sensitive patients.

It may be inferred from this experiment that (1) the presence of agglutinins was demonstrated in sera of known ragweed-sensitive patients; (2) the antigenic property of ragweed pollen was transferred to bacteria. However, the low titer of agglutination is not very conclusive.

It remains for further investigation to determine (1) if there are any other factors which may influence a fluctuation of the titer of agglutination of pollen-antigen-coated bacteria by sera of ragweed-sensitive patients; and, (2) if, after specific therapy in ragweed-sensitive patients, changes in the titer of agglutination occur.

If the above method can be improved for the detection of agglutinins in sera of known ragweed-sensitive patients against pollen-antigen-coated bacteria, then, perhaps, other agglutinins in other allergies may be demonstrated.

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### REFERENCES

- 1. Jones, F. S.: *J. Exp. Med.*, 46:303, 1927.
- 2. Roberts, E. C. and Jones, L. R.: *Proc. Soc. Exp. Biol. & Med.*, 47:11, 1941.

## MILITARY ASPECTS OF ALLERGIC RHINITIS

MAJOR PHILIP BLANK, MC

and

CAPTAIN HARRY LEVITT, MC

**A**N increasing interest in the problems of allergy by the armed forces<sup>3,5,8,16</sup> has been evidenced by the large number of allergy sections and clinics established in various Army hospitals and by the recognition of allergy as a medical specialty by the Navy. With this increased interest comes a need for more specific and detailed knowledge of the many difficulties that beset this new field of Military Allergy. It is the purpose of this paper to discuss the military problems involved in the study of allergic rhinitis.

Allergic rhinitis is a "harassing" disease. It causes tremendous loss of efficiency and may cause much loss of time. Soldiers suffering this affliction haunt the eye, ear, nose and throat clinics without much relief from their symptoms unless an allergic regime is instituted. This disease is often misunderstood in the various military organizations and gives the soldier not only a physical handicap but also a great mental hurdle to overcome. He is often branded a "goldbrick."

The term allergic rhinitis refers to a syndrome of sneezing, rhinorrhea, and nasal obstruction due to hypersensitivity to various antigens. It may be perennial or seasonal in nature. Many and various terms have been applied to this syndrome, some pertaining only to the perennial type of allergic rhinitis and others only to the seasonal type. Among these terms are found vasomotor rhinitis, perennial rhinitis, paroxysmal rhinitis, allergic coryza, allergic rhinopathy, hay fever, rose fever, summer catarrh, pollerosis and many others. No term suggested to date has been completely satisfactory to all, therefore, the terms used in this discussion are defined. The term allergic rhinitis will refer to all cases of rhinitis having an allergic etiology; perennial rhinitis will refer to those cases that are perennial in nature without undue seasonal variation and not due to pollen and the term hay fever will refer to seasonal allergic rhinitis due to pollen. The term hay fever may be qualified by adding the name of the season in which it occurs or by the name of the plant which produces the pollen. This choice of terms is only because of popular usage and simplicity.

The military problem of allergic rhinitis involves not only the diagnosis and treatment of these cases, but also the applicability of treatment and the disposition of these patients. In other words, what should be done with a soldier suffering from allergic rhinitis and what prognostication can be made concerning his reaction in various places under various conditions.

The incidence of allergic rhinitis among military personnel is noted

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TABLE I. CASES OF ALLERGIC RHINITIS SEEN AT FORT EUSTIS, VIRGINIA  
(June 1, 1941 to December 31, 1943)

	Number of Treated Cases	% of Total Cases	Incidence per 1000 Men
Fall hay fever	303	41.0%	2.58
Fall hay fever and perennial rhinitis	22	3.0%	0.19
Fall hay fever and asthma	39	5.4%	0.33
Fall hay fever, asthma and perennial rhinitis	1	0.1%	0.01
Summer hay fever	75	10.2%	0.64
Summer and fall hay fever	60	8.1%	0.51
Summer hay fever and perennial rhinitis	13	1.7%	0.11
Summer hay fever and asthma	14	1.8%	0.13
Summer and fall hay fever and perennial rhinitis	9	1.2%	0.08
Summer and fall hay fever and asthma	13	1.7%	0.11
Perennial rhinitis	155	21.0%	1.32
Perennial rhinitis and asthma	37	4.8%	0.31
Total	741	100.0%	6.32

in Table I. In this table the various syndromes and combinations of syndromes are tabulated. They represent only the group of cases seen at the Allergy Clinic at Fort Eustis, Virginia, from June 1, 1941, to December 31, 1943.

A total of 741 cases of allergic rhinitis was seen at this clinic and represents an incidence of 6.3 per 1,000 men. Although this figure is lower than is usually quoted as the incidence of allergic rhinitis, it must be remembered that many of the more severe cases are rejected for military service by the induction boards and many of the milder cases do not report for treatment or are not recognized as allergic sufferers. Therefore the figure 6.3 per thousand does not accurately represent the incidence, but rather represents the number of men who received allergic care because of allergic rhinitis at Fort Eustis, Virginia.

Clinically uncomplicated fall hay fever due to ragweed pollen represents 41 per cent of the allergic rhinitis cases. These cases had no clinical manifestation of sneezing, nasal congestion or rhinorrhea at any time except during fall hay fever season. Of these 303 cases, 100 cases showed marked or moderate skin sensitivity to ragweed pollen alone, while 193 cases showed moderate or marked skin sensitivity to other inhalants. Forty-six cases showed a greater skin sensitivity to other inhalants than to ragweed pollen, while ten cases showed no skin sensitivity at all. However, these latter cases showing no skin sensitivity showed sensitivity of the nasal mucosa or conjunctiva or both to ragweed pollen on contact.

Twenty-two cases of fall hay fever were complicated by evidence of perennial rhinitis. These cases were all clinically fall hay fever but on close questioning gave a history of attacks of allergic rhinitis at times other than the hay fever season.

Thirty-nine cases of fall hay fever were complicated by asthma, seventeen of these cases had seasonal asthma coming on towards the end of the season while twenty-two cases had occasional mild perennial asthma. The latter cases were not classified primarily as asthma because of the

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mildness and the infrequency of their asthmatic symptoms. These patients gave a history of wheezing only on close questioning and the majority of them did not realize they had asthma. Ordinarily this type of rhinitis would pass as simple hay fever. It is important from a military standpoint to distinguish complicated from uncomplicated cases because of the effect of nonspecific factors in the future behavior of these men.

Sixty cases gave clear-cut histories and findings of both grass and ragweed hay fever with a period of relief between two attacks.

Summer hay fever due to grasses was found in seventy-five cases. These patients had no symptoms except during the season of grass pollination but again many multiple skin sensitivities were found. The incidence of multiple skin sensitivities was greater in this group than in the ragweed group. Although the summer hay fever cases were on the whole clinically milder than the ragweed cases, more complications such as perennial rhinitis and asthma were found. There were more clinically complicated cases of summer hay fever (109 cases) in relation to clinically uncomplicated cases (75 cases) than there were clinically complicated cases of fall hay fever (122 cases) in relation to uncomplicated cases of fall hay fever (303 cases). The grass hay fever cases represent a more difficult problem to our overseas forces than do the ragweed hay fever cases because of the more universal distribution of grasses and the higher incidence of complications in this group.

In this clinic spring hay fever due to trees was not seen except for one case of oak sensitivity combined with grass sensitivity. We feel that this is purely coincidental and a result of the short duration of the tree season. A few cases due to molds were seen but the clinic was inadequately prepared for intensive mold studies and therefore this group of cases is not reported in this paper.

One hundred fifty-five cases of perennial rhinitis were seen in this clinic. The majority of these cases were due to inhalants only, there being only twelve cases which were definitely proven to be due solely to foods. Studies for bacterial antigens were unsatisfactory because of the lack of bacterial antigens on hand. Most cases were sensitive to dust but clinical sensitivities to pyrethrum, feathers, orris root, pine sawdust, tobacco, and animal danders were rather frequent.

All cases of perennial rhinitis received an x-ray study of their sinuses. In all but twenty cases evidence of pathology in the sinuses was found on x-ray examination, and was mainly evidenced by a thickening of the mucous membranes; hypertrophic sinusitis. Some degree of polyposis was found in thirty-two cases. Two cases of perennial rhinitis were associated with a generalized pruritis which disappeared during treatment of the rhinitis without local or any other general treatment. One case of perennial rhinitis was associated with a marked seborrhea; both conditions were controlled by the elimination of cottonseed oil, corn and grapefruit from his diet.

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The cases of perennial rhinitis with asthma represent those cases having had only very slight wheezing attacks, this symptom being elicited only on detailed history. This group probably should be listed as extremely mild asthmatics but because their symptoms were practically entirely upper respiratory they are listed as rhinitis cases rather than asthmatic cases.

In military allergy, as well as in civilian practice, the precise etiologic diagnosis of hay fever requires a knowledge of the pollens to which the patient is exposed. This requires a knowledge of the identity of those plants in the patient's vicinity which are capable of producing symptoms. It is not only necessary to know the identity of plants but also their relative prevalence and the average onset and termination of their pollinating seasons. The military surgeon dealing with allergic diseases must have some knowledge of the plant flora in any locale that the Army finds itself. Thus, in this day of universal warfare, a knowledge of the plant flora throughout the world is necessary. An attempt has been made in a general way to tabulate the more important causes of hay fever in various parts of the world with the realization that such a tabulation must be extremely general because of the lack of material from many parts of the world and the lack of space in a paper such as this. Nevertheless, for clinical and practical purposes, single cities or areas are taken as typical for large districts to contain a certain type of flora with pollination seasons which with some variation are by and large uniform for that area.

Pollen data for the United States<sup>7,10</sup> are abundant and easily obtained. The main facts concern ragweed and grasses, but it must be remembered that many other plants, trees, and molds can be important factors in the etiology of hay fever.

Ragweed is found in a belt bounded roughly by the Great Lakes and the forested area north of them, the Appalachian Mountains, the Gulf of Mexico and the hundredth meridian, with the heaviest recorded production in Indiana. Most of the ragweed pollen is produced by short ragweed and giant ragweed. The other ragweeds are mainly of local or sectional importance. While western and false ragweed may begin pollination in the southwest as early as May 15 the real ragweed season begins abruptly during the second week of August in the whole area east of the Rocky Mountains and north of Arkansas and Tennessee. In the southern states the onset of the season is from one to four weeks later than in the north. The pollen storm reaches its height earliest in the high dry region of the upper Missouri Valley about August 25, which is about a week earlier than in the north half of the Mississippi Valley and the Great Lakes region. By the first of September the center of the storm has begun to move southward reaching south Texas about October 1. The early approach of cool weather in the Dakotas, Montana and Wyoming limits heavy ragweed pollen production to about thirty

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days. The average length of the season in the central and southern states is from forty-five to fifty days, with an extreme range of possible exposure of very sensitive hay fever sufferers in Brownsville, Texas; southern Arizona and northeastern Mexico of six months, May 15 to November 15.

Grasses are almost universal in their distribution. There are many species of grasses, the more important being Timothy, Bermuda, June, Orchard, Johnson, Red Top and Sweet Vernal grass. It is usual to find Timothy grass predominating in colder or temperate climates and Bermuda grass predominating in the warmer areas. The period of pollination depends on the climate; for example, certain grasses may be perennial pollinators in southern California while others have a definite period from May through June in some of the more northern states. The reader is referred to the many excellent papers concerning plant pollination in the United States for more detailed data.

Outside of the United States the main offender producing hay fever is grass pollen. Ragweed<sup>1</sup> is seldom, if ever, found in Alaska, British Isles, Scandinavia, Belgium, Holland, Germany, Portugal, Spain, Italy, India, Burma, the Malay Peninsula, Indo-China, China proper, the Philippines, Egypt, South America or Africa. In general, the colder countries have a high proportion of Timothy grass and the warm countries have a preponderance of Bermuda grass. Trees and local vegetation are factors usually of minor importance except in definite localities. The main offenders are here noted in a rather general summary.

In the British Isles<sup>17</sup> the pollen season extends from February to the end of October and falls into three main phases dominated by trees, grasses and herbaceous dicotyledons, respectively. Of the trees the most important are Birch, Yew, Oak, Elm, Hazel and Alder. The tree season extends to about the end of April. The grass season starts early in June, reaches a peak late in June and extends to about the end of July. The grass season is by far the main hay fever season. The herbaceous dicotyledons are of minor importance.

Grass pollen is the greatest offender in Australia.<sup>6,20</sup> The season extends from September to December. Plantain rates second to the grasses as an offender and pollinates in practically the same months as the grasses. The trees pollinate in July and August, but are of slight importance since their pollinating periods are only of two to three weeks' duration.

In New Zealand<sup>14</sup> the grasses begin to pollinate near the end of November, reach a peak in January and terminate by the end of February. The trees pollinate from August through October, the highest pollen counts furnished by *Pinus insignis*, *Macrocarpa*, *Sycamore*, *Oak*, *Tutu*, and *Silver Birch*.

H. J. Hara<sup>13</sup> states that it is interesting to note that there have been no cases of pollinosis reported in Japan, although vegetation such as

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grasses, lambs quarter and cereals is plentiful. The people of Japan have always been free from hay fever, although other allergies are as frequent as in other parts of the world.

Hay fever in most of the South Sea Islands is practically an unknown quantity. From Hawaii there is reported a perennial yield of grass pollen, algroba or kiawi tree pollen and some monkey pod tree pollen.

Gutmann,<sup>12</sup> in 1942, reported hay fever in Palestine. He found Bermuda grass of greatest importance being perennial in nature. He states that a special peculiarity of the country is the wide distribution of citrus plants. The "stupefying" odor of the blossoms in April and May in the vicinity of the orange groves occasionally forces even healthy persons to evacuate the vicinity for a time.

The cause of hay fever in South Africa<sup>21</sup> is also mainly Bermuda grass plus some of the tall veldt grasses (*Eragrostis plana*). The compositae are abundant and occasionally cause trouble as do the mimosa (*Acacia robusta*), lambs quarter (*Chenopodium album*) and the pepper tree (*Schinus molle*).

On the European mainland the most common offender is also grass. In Denmark<sup>2</sup> the pollination of grasses starts the first week of June, reaches a peak in the third week of June and ends in the last week of July. According to Landau and Gay,<sup>19</sup> the absence of ragweed is the outstanding feature in European hay fever. In Germany<sup>19</sup> allergy to linden accounts for 10 to 20 per cent of all hay fever cases. Allergy to hazelnut, willow and poplar is fairly common. The more important fungi in Germany are *Aspergillus fumigatus*, *Aspergillus niger*, *Penicillium glaucum*, rusts and smuts. The vast majority of hay fever cases however, result from grass sensitization. From Prague, in Czechoslovakia, Hlavacek and Blattney<sup>15</sup> report the grass season from the end of May to early in July.

Gay, Curtis and Norris<sup>9</sup> report that in Bermuda there is only one offending pollen of clinical importance, that being the cedar (*Juniperus bermudiana* L.). A cedar pollen sensitive patient suffers five weeks from late February to early April. Although grass and plantain are present, clinical observations of the inhabitants and visitors confirm the general opinion that grass pollen and plantain pollen hay fever is unknown or of no clinical significance. No ragweed is found in Bermuda.

In Brazil<sup>11</sup> there is only one hay fever season of clinical importance. It continues through the last two weeks in May and the first week in June. This pollen season is that of the grasses with Bermuda grass predominant.

From personal observation in North Africa, Italy and Sardinia, grasses are the most important causes of hay fever. This observation is confirmed by studies made by Kalisch in Italy and Weitz in North Africa. The main season occurs in the latter part of April and extends through June, although some cases are seen as late as the end of August or the beginning of September.

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The main offenders of perennial rhinitis may be divided into two groups, first, the specific factors and second, the nonspecific factors with which the soldier comes in contact. The specific factors are mainly inhalants and consist of house, barracks and tent dusts, wool, cotton, feathers, tobacco, pyrethrum, soaps, toilet articles, straw dust, newspaper dust and sawdust. Other factors such as horse dander in the horse cavalry and animal danders in those outfits having animals as mascots are found in particular units. Flying personnel come in contact with rabbit and wool linings in their flying clothes, and kapok lining in certain types of planes. Kapok can be a factor on transports using life preservers made from this material. Occasional cases, with foods as specific etiological factors, are found.

Nonspecific factors such as sudden changes in temperature, irritating odors, vasomotor changes due to psychic causes, extremes in humidity, sudden changes in humidity, physical and mental exhaustion, and infections may be the aggravating cause of perennial rhinitis. In occasional cases some of these nonspecific factors may be the specific factor, viz., bacterial allergy and physical allergy.

The prodromal symptoms of allergic rhinitis consist of a feeling of weakness, depression and irritability. The patient frequently complains of vague disturbances of the eyes, nose, and ears, digestive sluggishness, drowsiness after meals and occasional localized or generalized itching. Symptoms may develop slowly or acutely; the former is more common in cases of perennial rhinitis while the latter is more common in cases of hay fever.

The patient has a distressing urge to sneeze, sneezing occurring in paroxysms of ten to fifty sneezes, and at times causing almost complete exhaustion and pain in the chest. Itching of the nose may be intense and is often accompanied by a burning or tickling sensation of the nose and the roof of the mouth. There is a rhinorrhea of a clear, watery fluid, at first containing only a few cells and later containing more cells and becoming mucoid. The secretion is usually nonirritating although the nose may become irritated from the mechanical effect of wiping. Nasal obstruction is common but not constant. It is due to the edema of the mucosa lining the turbinates. Patients frequently complain of nasal obstruction on the dependent side of the nose while lying down. Post-nasal drainage unassociated with anterior rhinorrhea is common in chronic cases of perennial rhinitis. Partial deafness may result from edema involving the eustachian tubes. These cases may present retraction of the ear drums and the patient may complain of earache. Frontal or antral headaches or a feeling of heaviness may result from mouth breathing produced by nasal obstruction. There may be some heaviness and constriction of the chest with or without dyspnea. These are warning signals of impending asthma. Approximately one-third of all patients with allergic rhinitis will develop asthma if allowed to go untreated.

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Eye symptoms are very common in allergic rhinitis and consist of itching, sandy feeling of the lids, reddening of the conjunctiva, lacrimation and photophobia. Pain is not a constant finding; in fact it is found in a much smaller percentage of cases than one would expect upon noting the apparent pathology. The symptoms result usually from a conjunctivitis; however, keratitis<sup>4</sup> is not an uncommon finding; the ulcers are marginal, being about one to two millimeters from the limbus. At first they are discrete and usually involve just one quadrant, later they become larger, coalesce, involve the entire perimeter of the cornea, and finally result in a continuous marginal ulcer. A secondary central ulcerative keratitis may result from a lack of nutrition. Itching is intense and pain very mild. Iritis, uveitis, and retinitis have been noted.

Cutaneous manifestations are quite frequent. Generalized or localized pruritis will often usher in an attack of hay fever. Two cases of allergic rhinitis were seen whose main complaint was that of generalized itching with minimal nasal symptoms. Contact dermatitis due to pollen or other antigens is occasionally seen in conjunction with allergic rhinitis.

Systemic manifestations of weakness, lassitude and mental depression are frequently found. Fever is rare, anorexia and belching common.

In the early stages the nasal mucosa appears swollen and boggy, the color varies with the stage and duration of the process. It may be normal, slightly pale, markedly pale, bluish, pinkish, gray or red. In more advanced cases, there is thickening, hyperplasia and polypoid degeneration of the epithelium. Microscopically there is marked eosinophilic infiltration of the epithelial and the subepithelial structures, more advanced cases showing thickening, hyperplasia and polypoid degeneration of the epithelial layer with eosinophilic infiltration, edema, varying amounts of mononuclear, round cell, and lymphocytic infiltration and connective tissue proliferation. The blood vessels may be dilated, compressed or thickened, while bone may present either hyperplastic or atrophic processes. The periosteal layer shows round cell infiltration and connective tissue proliferation. Secondary infection modifies this picture.

The diagnosis of allergic rhinitis depends mainly on the history of recurrent bouts of sneezing, rhinorrhea and nasal obstruction. The diagnosis is confirmed by laboratory means including such procedures as eosinophile counts of the circulating blood, eosinophile studies of nasal and eye secretions, various types of skin tests, direct contact tests to the nasal mucosa and conjunctiva, passive transfer tests and dietary studies. This entire group of tests is seldom available to most military medical installations, especially overseas installations. Advanced front line installations have no, or at the very most, very limited laboratory facilities. Here the diagnosis must be tentatively made from the history and, at most, from the eosinophile count of the blood and secretions, and from the observation of the patient. Further to the rear, unless the hospital has an allergy section, the laboratory facilities will not include

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specialized allergy tests. Most army allergy sections are inadequately supplied to do complete allergy studies. Again this is especially true of overseas installations. However, the vast majority of army allergy clinics are conducted by men especially interested in the military problems of allergy. These men, many of whom are well-trained allergists, are getting materials in many ways. It is difficult to do adequate dietary studies in most overseas hospitals because of the lack of foods and the absence of allergy kitchens.

The treatment of allergic rhinitis consists of elimination of the offending agent, hyposensitization and local treatment. Medical judgment as to the treatment of these cases, however, often differs in military therapy from civilian therapy. Elimination procedures are often difficult, if not actually impossible; hyposensitization routines can be impractical and local therapy may not be efficacious. In this paper only the military aspects of treatment will be discussed.

Forward echelons should evacuate cases of allergic rhinitis to the nearest allergy clinic in the rear echelon for study and disposition. The use of local measures such as ephedrine solutions or oils intranasally, inhalers of various types or oral preparations of ephedrine, atropine and sedatives will usually suffice to give the soldier relief until he is evacuated. On missions, men who suffer from allergic rhinitis can be dangerous to his fellow soldiers, such a case was seen by Capt. A. C. Kalisch, MC.<sup>18</sup> A mortar detachment was ordered to wipe out a gun position in one of the hills of Italy. These men proceeded to climb to an advantageous position, without giving themselves away to the enemy. As they were digging in, one of the members of the detachment began a bout of sneezing. The enemy then noting this new mortar position immediately trained machine gun fire on this little group and caused three casualties. Men with allergic rhinitis cannot be used where secrecy is paramount. This applies especially to reconnaissance troops of various sorts, litter bearers, snipers, troops on special missions, etc. It is our opinion that no case of allergic rhinitis should be in actual fighting positions because first, these men are not dependable, having periods of marked inefficiency due to sudden and often unpredictable bouts of sneezing and second, there are so many places where these men could serve a useful purpose that it is unnecessary to assume the risk and the treatment of these cases under such adverse conditions.

After the allergic case has been evacuated to an allergic section, it becomes necessary to decide what type of therapy and what disposition of the soldier should be made. This of course depends on where the patient is and what the local conditions are.

Seasonal hay fever due to trees uncomplicated by other clinical sensitivities need very little care except local therapy unless the symptoms are very severe, in which case hospitalization for the short time necessary for the cessation of his symptoms is recommended. Grass hay

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fever cases offer a much more difficult problem because it must be remembered that these men are lying in the grass, sleeping in grass, and walking through grass so that there is very intimate contact with the offending agent. Thus, pollen counts will not reflect the actual conditions of pollen saturation encountered by the soldier. These men should be hyposensitized and reassigned. They should not do front line work regardless of the apparent degree of severity because mild cases can easily become severe under the very adverse conditions "up front." He need not be designated as limited duty but simply put in a rear echelon as general duty. The hyposensitization should be perennial because, during the fast movement of troops, the season may vary so as to leave him unprotected if only preseasonal measures are used. Parenteral treatment is at present more satisfactory than oral therapy; however, the limitations of oral therapy should be further studied and if possible, adjusted to military needs. Oral therapy would be of tremendous value in the treatment of allergic disease in the army.

Hay fever cases complicated by clinical perennial rhinitis or asthma should receive treatment for both conditions and be classified to limited duty. It is preferable to keep these men on duty within the continental limits of the United States.

Uncomplicated cases of perennial rhinitis should be placed only in rear echelons and never in "front line" positions and if complicated should be on limited type of duty within the United States.

Uncomplicated ragweed hay fever cases will do well overseas, but should not be designated for battle duty, because of the possibility of transfer of sensitivity to other antigenic substances with subsequent breakdown. Complicated ragweed cases should be kept within continental limits of the United States and, if feasible, sent to low ragweed pollen areas such as southern Florida or west of the Rocky Mountains. All cases of ragweed hay fever should receive perennial hyposensitization. It would be advantageous to have a copy of the treatment record accompany each man on troop movements to be delivered to the next station for continuation of therapy. It has been unsatisfactory to classify hay fever according to the degree of severity because such a classification depends on the personal opinion of the examiner and the history of the patient. The severity of hay fever is reflected in the history of the case in direct proportion to the anticipations and desires of the patient; if the examination is for a pleasant assignment the patient minimizes his symptoms, otherwise he exaggerates them. The severity of hay fever also depends on the pollen counts, intimacy of contact and various non-specific factors. We feel that no case of uncomplicated seasonal hay fever need be separated from the service.

The military treatment of soldiers in the United States does not offer the problems of overseas treatment. The prime object of an allergy section in the United States should be to prevent soldiers with allergic

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conditions from getting to places where they will be a burden. It is absolutely essential that there be close co-operation between the medical and the personnel sections. These soldiers afflicted with the various allergies can do good work, but they cannot do it under all conditions. This fact must be recognized and proper emphasis placed upon it.

It has been the purpose of this article to bring to light more of the detailed problems of military allergy, especially the problem of allergic rhinitis and to try to offer in general, a workable solution. It is well recognized by the authors that in time of peace with a small standing army, the problem of allergy is minimized; but, during times of stress with the need of all available manpower, it becomes essential that we do not discard a group of men that are capable of performing useful, efficient work for the services. While the existence of allergic rhinitis has been recognized, the military attitude has been to shy away from this group of cases and to allow those men who are interested in delving into the problem of allergy to do so unofficially. Statistics of allergic cases in the army in previous wars are very unreliable because no definite mention is made of allergic rhinitis. The terms used at present, as found in the various extracts of regulations of sick and wounded, are hay fever, rose cold, polypus nasal, and rhinitis acute, atrophic, membranous and hypertrophic. From these diagnoses it would be extremely difficult to get a true evaluation of the statistical report of allergic rhinitis in the army. Thus the problem of allergic rhinitis finds only a tiny niche among the problems of the Surgeon General because statistically he has little on which to base official action.

### SUMMARY

1. The incidence of allergic rhinitis at Fort Eustis, Virginia, was found to be 6.3 per thousand men.
2. Emphasis is placed on the differentiation between complicated and uncomplicated cases of allergic rhinitis.
3. A general outline is presented of the pollen conditions in the various parts of the world.
4. The military treatment and disposition of cases is suggested.

### REFERENCES

1. Allard, H. A.: The North American ragweeds and their occurrence in other parts of the world. *Science*, 98:292, 1943.
2. Baagøe, K. H.: Polleninhalt der Luft in der Heufiebersaison, *Acta Med. Scandinav.*, 84:217, 1934.
3. Blank, P.: Military aspects of allergy. *J. Lab. & Clin. Med.*, 28:609, 1943.
4. Blank, P.: A survey of allergy in a station hospital. *Mil. Surgeon*, 92:419, 1943.
5. Crandall, F. G., Jr.: Allergy in military medicine. *Mil. Surgeon*, 87: No. 4, (Oct.) 1940.
6. Derrick, E.: Notes on causes of hay fever and asthma in Australia. *Med. J. Australia*, 2:603, 1929.
7. Durham, O. C.: The pollen content of the air in North America. *J. Allergy*, 6:128, 1935.

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## SEVERE LIGHT HYPERSENSITIVENESS CURED BY CHOLECYSTECTOMY

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IT IS a fairly well-established fact that the treatment of a hepatopathy, a gastro-intestinal disease, an endocrine dysfunction, a focal infection, or an intoxication will prove to be beneficial in many cases of light hypersensitivity. Such therapy is often followed by a complete cure or at least a temporary disappearance of the cutaneous disease caused by light. It is now generally believed that these results may be attributed to the fact that the formation of photosensitizing or photodynamic substances is more or less completely checked by the elimination of the underlying disturbance.

Thus, in a case of hydroa vacciniforme, Urbach and Bloech<sup>20</sup> observed that antiluetic therapy which improved the patient's syphilitic hepatitis resulted in a disappearance of the concurrent porphyrinopathy. Barber<sup>1</sup> described a patient who acquired light dermatitis by exposing himself to sunlight after overindulging in alcohol. His liver was greatly enlarged. A strict diet and complete abstinence from alcoholic beverages caused improvement of the liver condition and an early cure of the photosensitivity. Barber, Howitt and Knott<sup>2</sup> reported a number of cases in which treatment of a gastro-intestinal disease was followed by marked retrogression of skin manifestations produced by light. These authors expressed the opinion that the light hypersensitivity was attributable to a bacterial toxin formed in the intestine. D'Amato<sup>5</sup> observed a woman whose skin lesions appeared only during her menstrual period. Following temporary inhibition of menstruation by roentgen irradiation, the patient's manifestations of light hypersensitivity disappeared, but recurred some months later when menstruation returned. Lancaster<sup>7</sup> observed five cases in which the correction of menstrual disturbances, by the administration of estrogenic substances, was followed by a permanent restoration of tolerance to sunlight. Similar observations have been reported by Thurman<sup>17</sup>, Brunsting<sup>4</sup>, and also by one of us (E. U.).<sup>19</sup> Stokes and Callaway<sup>16</sup> have called attention to the development of sensitivity to light in patients with either systemic or local infections. Sonck<sup>15</sup> reported a case of light hypersensitivity in a patient suffering from lymphogranuloma inguinale; following a radical operation (extirpation of the rectum), the photosensitivity disappeared.

We wish to report a case in which the removal of the patient's diseased gall bladder was followed by the complete cure of a severe light dermatitis of nine years' duration.

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## LIGHT HYPERSENSITIVENESS—URBACH AND SHAY

Mrs. M. W. L., sixty-three years of age, enjoyed perfect health up to the age of fifty-one years. In July, 1932, she noticed that her skin (face, neck, back of the hands) became unusually red after exposure to sunlight; and that this reddening disappeared when she stayed at home for a few days. The skin was found to be definitely more irritable at the seashore than in Philadelphia, and in the late fall the reddening ceased altogether. Thereafter, each year, this light dermatitis recurred in the spring and regressed in late fall. In May, 1940, the patient took a long automobile trip, which brought on very severe inflammation and swelling of the exposed skin areas.



Fig. 1. Appearance of patient two hours following twenty minutes of exposure to July sunlight.

For many years, the patient had been complaining of vague abdominal pains and distention. In addition, she had had occasional attacks of excruciating pains under the right costal rib which often radiated to the shoulder blades. These she had considered as attacks of acute indigestion. The patient also complained of poor bowel function.

Her weight had decreased 20 pounds during the three preceding years.

Physical examination revealed a co-operative, highly intelligent patient, anxious to get well. Mouth in good condition. Tonsils not infected. Heart not enlarged. No murmurs. Blood pressure: 134/80. Weight: 153 pounds.

There was redness and slight swelling of the face, of the upper chest, and back of the hands.

After the skin manifestations had disappeared, the left side of the patient's face and neck were deliberately exposed to twenty minutes of July sunlight. Two hours later, the exposed areas presented severe reddening and swelling (Fig. 1). The right side, which had been covered with zinc ointment, remained normal.

By means of special light filters, whose wave lengths were selected to permit the partial absorption of the short and long waves, as well as of the ultraviolet rays of the visible and invisible sun spectrum (Urbach)<sup>19</sup>, it was determined that the patient's skin was hypersensitive only to the ultraviolet rays.

The high degree of the patient's sensitivity to light was illustrated by her developing a mild but definite redness of the exposed skin three hours after a sixty-minute exposure (6:15 p.m.-7:15 p.m.) in the very late afternoon on a cloudy day. This redness was observable during the next twenty-four hours.

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Examination of the abdomen revealed tenderness in the right upper and lower quadrants on slight palpation. The liver and spleen were not enlarged. Bile drainage showed a poor gall-bladder function and typical cholesterol crystals microscopically.

Microscopy of nonsurgical drainage bile has been very useful in the diagnosis of gallstones. The finding of both cholesterol crystals and calcium bilirubinate pigment has been found by one of us (H. S.)<sup>2,8,12</sup> to be pathognomonic of gallstones. Cholesterol crystals alone have been found when either stones or a strawberry gall bladder were present. Cholecystography confirmed the diagnosis of gallstones.

Liver function tests, keeping in mind their limitations, showed a normally functioning liver. The hippuric acid test gave a 75 per cent excretion in two hours after a 4 gram dose.<sup>9</sup> The bromsulphaline excretion test was normal. The vanden Bergh qualitative test was indirect, and the quantitative test showed 3/10 of a mgm. of bilirubin per 100 c.c. of blood. The fasting blood sugar was 103 mg. per cent.

The blood count showed a hypochromic, normocytic anemia (hemoglobin 72 per cent, red cell measurements at upper limit of normal). The sedimentation rate was normal. Basal metabolic rate: —12 per cent. Morning and evening specimens of urine were normal except for a faint trace of albumen in the evening specimen.

Gastric analysis: Fasting: free HCl 22, total acid 38. Sixty minutes after Ewald breakfast: free HCl 30, total acid 50. No bile or blood was present.

Fermentation studies of the stools failed to reveal any abnormal fermentative or putrefactive changes in the bowels. Benzidine test for blood in feces was negative.

Porphyrin study in feces: ether extract and HCl extract showed a marked fluorescence with ultraviolet light.

Dried smear of feces: Ratio of 3 to 1 of Gram-negative to Gram-positive organisms. Type of bacteria: Small Gram-negative organisms—some coccoid—some in short chains. Moderate number of Gram-positive cocci in pairs. A few large thick Gram-positive rods, single and short chains. A few large slender Gram-positive rods, single and in short chains. Fat: not present. Starch: negative. Muscle fibers: none noted. Numerous vegetable fibers.

Bacteriology: (a) Aërobic Blood agar plates showed the predominant organisms to be *Streptococcus viridans*. However, relatively few bacteria grew as compared with a normal fecal flora. Endo and Sabouraud plates show essentially the same findings.

(b) Anaërobic. Blood agar plates showed heavy growth chiefly bacteriodes, occasional *B. coli* hemolyticus and few indifferent streptococci. Deep meat culture showed marked digestion.

Stool cultures, therefore revealed a preponderance of *Streptococcus viridans* and a very scant growth of aërobic bacteria. On the other hand, the anaërobic flora was heavy with bacteriodes as the leading organisms. These findings indicate that the flora of the intestine was pathologic.

Twenty-four hour output of porphyrin in urine and stool after the patient had been on a meat-free diet showed a slight increase over normal of porphyrin in the stool and a normal output in the urine.

Since the usual dermatologic methods to protect the patient against light were ineffective and since medical management failed to control the gall-bladder condition, the gall bladder was removed on April 10, 1941, by Dr. William Bates. The gall bladder showed evidence of chronic disease, contained stones of the mixed type, and the gall-bladder wall was thickened. Gram-positive cocci were found in a stained smear of the bile but culture of the bile yielded no growth of organisms.

Four weeks after the removal of the gall bladder, the patient exposed herself

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to sunlight. While her light sensitiveness showed very definite improvement, a slight rash did develop on her face, neck, and arms. However, three months later (July, 1941), the patient was able to sit in the sun without any abnormal skin reaction resulting. Since then, now nearly four years, there have been no recurrences of the skin rash despite frequent exposure to strong sunlight at the seashore. There have been no gastro-intestinal symptoms since the cholecystectomy. A recent twenty-four-hour stool and urine porphyrin determination yielded normal results.

### DISCUSSION

In the introductory paragraph of this paper, a few examples were cited to demonstrate that light hypersensitivity may be brought about by a great variety of conditions. Our understanding of the true nature of the mechanism involved is, as yet, sketchy at best. However, in a number of instances, there is good reason to believe that the primary disease brings on a porphyrinopathy, which, in turn, creates hypersensitivity to light.

In our patient, an infected gall bladder was, in all probability, the primary cause of the actinic dermatitis. The literature contains reports<sup>6,12,14</sup> which show that cholecystitis may be the sole cause of certain skin diseases in which extirpation of the gall bladder was followed by a disappearance of the skin lesion.

Unfortunately, we are unable to present any data that would establish the mechanism by which the diseased gall bladder caused the skin sensitivity to light in our patient. Certain theoretical considerations are presented, therefore, with due regard for the breach in our evidence to support them.

The rapid and complete restoration to normal of the patient's skin reaction to light after cholecystectomy naturally offers the removal of a focus of infection as a possible explanation for the result. The removal of such a focus, if it were a source of some sensitizing agent for the patient's skin, could result in a cure.

Another possibility might be considered. A twenty-four-hour stool and urine output of porphyrin did show a slightly increased amount over normal in the stool but no alteration from normal in the urine. Recent investigations in light dermatoses have shown the porphyrin content of the feces to be increased in the presence of certain pathologic intestinal flora, notably with a preponderance of streptococci over *Bacterium coli* (Urbach).<sup>18</sup> It is noteworthy that, in these cases, an increased porphyrin content will be found only in the stool, but not in the urine and blood. The porphyrins that are absorbed in the intestinal tract ultimately reach the liver by way of the portal system. Here the porphyrins are, in part, broken down or otherwise transformed; most of them, however, are returned to the intestinal tract in the bile (entero-hepatic circulation of the porphyrins).<sup>21</sup> But if the mucous membrane of the gall bladder is irritated, it is conceivable that the increased amounts of intestinal porphyrins brought to the liver may be resorbed from the

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bile through the inflamed mucous linings of the gall bladder, and so reach the general circulation in abnormal amounts, which, in turn, may eventually cause skin sensitization to light. A parallel for such activity by the gall bladder with respect to porphyrins may possibly be found in the concentration of bile salts in the bile by the normal gall bladder<sup>10</sup> and in the disappearance of bile salts from the contents of the diseased gall bladder.<sup>11</sup>

### SUMMARY

A case of severe light dermatosis which was cured by extirpation of the infected gall bladder is reported.

As in other cases of light hypersensitivity, a pathologic intestinal flora was found. This may well have been the cause of the increased porphyrin content of the stool.

Two possible mechanisms are suggested, through either of which the diseased gall bladder could have been responsible for the sensitizing agent causing the light hypersensitivity. These would also explain the rapid and apparently permanent clinical recovery from this hypersensitivity as a result of the cholecystectomy.

### REFERENCES

1. Barber, H. W.: Significance and pathogenesis of certain dermatoses. *Practitioner*, 128:209, 1932.
2. Barber, H. W., Howitt, E. D., and Knott, F. A.: Light sensitization. *Guy's Hosp. Rep.*, 76:314, 1926.
3. Bockus, H. L., Shay, H., Willard, J. H., and Pessel, J. F.: Comparison of biliary drainage and cholecystography in gallstone diagnosis with especial reference to microscopy. *J.A.M.A.*, 96:311, 1931.
4. Brunsting, L. A.: Discussion to Thurmon.
5. D'Amato, G.: *Fotopersensibilità della cute di origine innersecretoria*. *Policlinico (sez. prat.)*, 33:1750, 1926.
6. Goss, C. C.: Biliary disease as an etiologic factor in urticaria. *Northwest Med.*, 31:377, 1932.
7. Lancaster, A. H.: Estrogenic hormone therapy in sunlight eruptions of female. *South. M. J.*, 32:495, 1939.
8. Piersol, G. M., Bockus, H. L., and Shay, H.: The diagnostic value of duodenal drainage in gallstone disease. *Am. J. M. Sc.*, 175:84, 1928.
9. Probstein, J. G., and Londe, S.: Studies of liver function by means of Quick's hippuric acid test. *Ann. Surg.*, 111:230, 1940.
10. Ravidin, I. S., Johnston, C. G., Riegel, C., and Wright, S. L., Jr.: Studies of gall-bladder function. VII. The Anion-Cation content of hepatic and gall-bladder bile. *Am. J. Physiol.*, 100:317, 1932.
11. Riegel, C., Ravidin, I. S., Johnston, C. G., and Morrison, P. T.: Studies of gall-bladder function. XIII. The composition of the gall-bladder bile and calculi in gall-bladder disease. *Surg., Gynec., & Obst.*, 62:933, 1936.
12. Schur, H.: Urticaria and cholelithiasis. *Wien. klin. Wchnschr.*, 40:81, 1927.
13. Shay, H., and Riegel C.: The role of the laboratory in the diagnosis of gall-bladder disease. *Am. J. M. Sc.*, 192:51, 1936.
14. Shay, H., Gershon-Cohen, J., and Fels, S. S.: The factor of hepatic and biliary tract disease in some cases of allergy. *Am. J. Digest. Dis.*, 6:335, 1939.
15. Sonck, C. E.: Ueber die Photosensibilität bei Lymphogranuloma inguinale. *Acta dermat.-venereol.*, 22:suppl. 6, 1941.
16. Stokes, J. H., and Calloway, J. L.: Pyogenic relapse and sensitiveness to light in certain dermatoses; influence of factor of intercurrent infection. *Arch. Dermat. & Syphil.*, 36:976, 1937.

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# Editorial

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## STANDARDIZATION OF EXTRACTS

For years the standardization of extracts has been a debatable topic. Numerous methods of extraction and standardization have been used when making allergenic extracts for diagnostic and treatment purposes. The various commercial manufacturers of allergenic extracts as well as clinical allergists making their own extracts have been blissfully going along compiling statistics, none of which is comparable or uniform.

The Standardization Committee of the American College of Allergists was organized for the establishment of standards for allergenic extracts, and it is making progress despite the many handicaps of a global war. The Committee is primarily interested in investigations which may give a clue to the real nature of allergens, as this information is necessary if logical and practical methods of standardization are to be developed. The solution of this problem will mean far more than the mere "purification" of an allergen, laudable as that may be. In most instances the chemical nature of the allergens responsible for clinical symptoms is not known. In the case of ragweed we have been led to believe that aqueous extracts of allergens are proteins whose antigenicity depends on their nitrogen content, although it is now shown that the active antigens in ragweed pollen are not proteins but actually are a flavone-polypeptide-carbohydrate complex. Finally, it is probable that satisfactory methods of standardization will include both a chemical and biological assay of the allergen.

The progress of the Committee is evidenced in several ways:

1. Through the efforts of Dr. George E. Rockwell, Chairman of the Committee, a research fellowship paying \$1,500 a year to continue for two years, has been placed under the direction of Professor M. A. Logan, Department of Biological Chemistry, University of Cincinnati Medical School.

2. It is hoped that the work which will result from the fellowship placed under the direction of Dr. Charles F. Code of the Mayo Foundation (announced in the *ANNALS OF ALLERGY*, November-December, 1944), may among other things give additional information as to the action of allergens.

3. The Committee has the unselfish and wholehearted co-operation of a number of members of the College, some of whom are on the scientific staffs of pharmaceutical concerns making allergenic extracts. The College is fortunate in having allergists of international reputation working with the Committee and devoting much of their time to the subject of standardization of extracts.

4. The College has the assurance of Dr. M. V. Veldee, Chief of the Biologics Control Laboratory of the United States Public Health Service,

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of their co-operation in our endeavor to establish standards for allergenic extracts.

5. The Committee is actively working on the standardization of dust and pollen extracts, and we have every reason to believe that they have already made some very important advances along these lines. Out of this work, specifications should come which if met will give the assurance of uniform and comparable extracts.\*

When considering the importance of this subject, we plead to all allergists, who appreciate the great need for a satisfactory method of standardization of extracts, to co-operate with us in this endeavor.

STANDARDIZATION COMMITTEE

## EDUCATION IN ALLERGY

The Educational Committee of the College† is initiating an intensive, earnest, and vigorous program of undergraduate education in allergy. After a study of the different facilities offered in allergy education by the leading medical schools for both graduate and undergraduate students, it is plainly evident that the rapidly increasing importance of allergy in relationship to various diseases is not appreciated by the majority of teaching faculties. There is a failure in the teaching of physicians to apply allergy properly to their practice whether general or specialty. Many medical schools do not include the teaching of allergy at all, while others offer a few lectures and others have a very limited didactic and clinical course integrated with the department of internal medicine.

With these facts in mind, the Committee realized the enormous task confronting it. Obstacles are numerous. Many allergists who have had certification in medicine handed to them by virtue of their age, influence or past accomplishments feel that the teaching of allergy should be relegated entirely to the department of internal medicine.

Before discussing this phase, let us review evident conditions which are going to influence graduate education in the future. There are now fifteen specialty boards that have certified a total of more than 24,000 physicians. According to Dr. Victor Johnson, Secretary of the AMA Council on Medical Education and Hospitals, these specialty boards have about attained their maximum number. Specialists in tuberculosis, cardiology, allergy and gastro-enterology are certified by the American Board of Internal Medicine. The various boards have a ruling requiring a diplomate to limit his work to one specialty which has already resulted in specialists, who practice in small cities, where there are too few patients seeking a specialist's care, to complain about this limitation.

There is an increasing tendency to seek board certification, as shown by a survey made by the AMA Committee on Postwar Medical Service. Approximately three-fourths of Army physicians indicated that they were

<sup>†</sup>The names of the members of this Committee appear on the officers' page of this issue.  
<sup>\*</sup>In the May-June issue there will be an important announcement concerning standardization.

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already certified by one of the specialty boards, or were planning to take the examinations for them on resuming civilian practice. The Army and Navy, government agencies, medical schools and insurance companies are all emphasizing certification, so that those who are not diplomates are becoming increasingly apprehensive lest they find themselves at a disadvantage in postwar practice. Inspiring further increased certification is the fact that many county medical societies have urged board approval, believing that certification is a guide to the laymen and general practitioner when indicating the difference between the competent specialist and the man who claims to be one.

With time and distance becoming a negligible factor, the family physician is rapidly being replaced by many strategically located hospitals in smaller cities that have every facility and competent specialists.

The laudable program for raising medical educational standards by the Council on Medical Education and Hospitals is going to produce a demand in graduate education requiring increased teaching material and staffs, leading to certification, so that the supply is only going to be met by the increase in specialists.

These are imminent problems which the Council will have to solve by modifying their present restricted view limiting the establishment of separate boards for specialists in tuberculosis, cardiology, allergy and gastro-enterology or face the possibility of specialists in these fields setting up their own specialty boards. Any discrimination against such newly organized groups becomes a restraint of trade.

Since allergy now embraces about fifteen diseases, and some of the most important come under specialties entirely apart from internal medicine, allergy should be considered a specialty which must be correlated with every other specialty of medicine. With this policy, the College has been able to secure the hearty co-operation of some of the most outstanding specialists in other fields who are properly applying allergy to their practice or teaching it in medical schools. These include pediatricians, otolaryngologists, dermatologists, gastro-enterologists, immunologists and bacteriologists. These men are certified by their various specialty boards and have gone through all the disciplines of medicine required by an accredited medical school. Limiting the teaching of allergy to either medicine or pediatrics was a very narrow view which retarded allergy education before the College was organized. In whatever field allergy exists, undergraduate students and graduate students should be taught concerning it. It is well known that many internists doing allergy take care of allergic infants and most of them, who have no special pediatric training, do this very poorly, causing great discredit to allergy. This rightfully applies to every other specialty in which allergy is encountered in its daily practice. When establishing a broad teaching program, it therefore seems logical that the heads of the departments of dermatology, gastro-enterology, pediatrics, otolaryngology, et cetera, be sufficiently trained in the practice of allergy so that they

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may adequately teach the undergraduate student how to apply allergy procedures to his patients or specialty so that when he graduates, whether he chooses the specialty of allergy or not, he will be far better fitted to apply it to his practice as a result of receiving this type of special training, and if he desires graduate training in allergy, he will already have a good foundation.

The heads of these departments should be integrated under a committee representing these various specialties and not just under internal medicine.

With these problems in mind, the Educational Committee is arranging a practical and efficient, specific curriculum of what they consider to be minimum requirements for the teaching of allergy. Increased clinical facilities will be stressed, and not lectures.

The theme of this program is to have allergy considered as an integral part of each of the allied fields or specialties.

When the allergist has a problem that requires the consideration of one of the allied specialties, it is absolutely necessary that there be a common denominator or mutual ground of understanding or appreciation. These allergy problems can best be solved or managed by wholehearted co-operation and united approach, if allergy is to advance and results are to be more efficient.

F. W. W.

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*The Effect of the Injection of Histamine into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand.* Stead, E. A., Jr., and Warren, J. W.: *J. Clin. Invest.*, 23:233, 1944.

Injuries to the forearm and hand make the capillaries more permeable. The authors use a rise in hematocrit reading without corresponding rise in the protein concentration as an indication that protein was escaping from the capillaries. 0.15 mm. of histamine was injected into the right brachial artery and, for several minutes after this injection, samples of blood were withdrawn. The subjects complained of pain, swelling and stiffness in the hand and forearm, with this reaction being confined to the extremity used. The hematocrit reading and the hemoglobin concentration of the forearm blood increased but the protein concentration showed little change. Arterial occlusion, by a blood pressure cuff, showed a tendency for an increase in both the hematocrit reading and protein concentration. A reaction similar to that produced by histamine is not seen in uninjured tissue in the usual types of shock.

*The Influence of Certain Amino-acids on Histamine Reactions and Anaphylactic Reactions in Intestinal Strips of Guinea Pigs and in Intact Guinea Pigs.* Landau, S. W., and Gay, L. N.: *Bull. Johns Hopkins Hosp.*, 74:55, 1944.

The authors used arginine monohydrochloride and histidine monohydrochloride in the successful prevention of the effect of histamine and/or antigen on the intestinal strip of guinea pigs. The action of acetylcholine was not suppressed by these amino acids. Death from histamine injection can be prevented in guinea pigs by the previous protection afforded by arginine; but this substance did not protect against death in anaphylactic shock in similar doses. Arginine was found to be highly toxic in high dosages. Skin reactions were not affected by the use of 2 per cent arginine.

L. J. H.

# Progress in Allergy

## ANNUAL CRITICAL REVIEW OF THE RECENT LITERATURE ON BRONCHIAL ASTHMA

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The previous survey of the literature included a study of most of the articles on bronchial asthma up to about October, 1943.<sup>104</sup> The present review covers the period from October, 1943, to the end of December, 1944, but also mentions a few foreign papers which did not become accessible until recently.

Many articles continue to appear, many of which are merely reviews. New data has appeared on the military aspects of allergy, and some important, even sensational, work has been carried out in the condition now known as "Tropical Eosinophilia."

### TROPICAL EOSINOPHILIA AND LOEFFLER'S SYNDROME

Within very recent years an apparently new condition has been discovered which Weingarten<sup>109</sup> has labelled "Tropical Eosinophilia." The condition usually begins insidiously, with malaise, low-grade fever, and headache. This period lasts about a week and usually leaves the patient weak and listless. An unproductive cough follows after a period of a few days to several months, and wheezing and dyspnea are often associated. Patients state that they have "asthma." The spleen becomes palpable, and x-ray films of the chest usually show a fine mottling of bronchopneumonia type in both lungs. Unless treated specifically with arsenicals, the condition may become chronic. No fatalities have occurred.

Leukocytosis (up to 60,000) and marked blood eosinophilia (up to 89 per cent) are striking features. A lesser degree of eosinophilia is also found in the sputum.

Tropical eosinophilia has become frequent among both civilians and soldiers in the Bombay region of India. It has also been found on the seaboards of Malabar, Coromandal, Gujarat, and Kathiawar. There is some doubt of its existence in other tropical regions, e.g., Porto Rico. It has been found in soldiers and civilians returning from the tropics, and therefore it is important that we recognize it. This is all the more necessary because one to six intravenous injections of such arsenical preparations as neoarsphenamine or novarsenobillon (N.A.B.) are specific. The symptoms abate at once, and the leukocytosis and eosinophilia disappear. Recurrences can occur. Oral administration of arsenicals, e.g., carbarsone, has also been effective.<sup>29</sup>

The fact that arsenicals cure the condition suggests that the disease is due to spirochetes or to protozoa, but search for these has so far been unsuccessful. All tests for parasites in the blood, urine, stools and sputum have been negative. Credit for the brilliant results obtained in tropical eosinophilia go to Weingarten<sup>109</sup>, Heilig and Visveswar<sup>50</sup>, Owen<sup>72</sup>, Vaidya<sup>107</sup>, Emerson<sup>29</sup>, and Apley and Grant.<sup>3</sup> Fenner<sup>32</sup>, from Australia, describes a case of "eosinophilic leukemia and asthma"—the fact that this soldier had an enlarged spleen and 60,000 leukocytes, with 74 per cent eosinophiles, would suggest the diagnosis of tropical eosinophilia. It would be interesting to see if injections of arsenicals would cure the patient. Unless there are definite contraindications, it would seem logical to try arsenicals in the treatment of asthmatic patients who have a very high blood eosinophilia.

In the differential diagnosis of tropical eosinophilia, one must consider worm infestations, Loeffler's syndrome, Hodgkin's disease, malignancy, and allergic bronchial

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asthma. In worm infestations the cause is usually found sooner or later. In trichiniasis the fever is apt to be higher at first, and ova can usually be found in the stool and the worm in the muscles; arsenic is of no help. Hodgkin's disease rarely has such a high percentage of eosinophiles and seldom more than 10,000 white cells. True allergic bronchial asthma likewise rarely, if ever, displays marked leukocytosis with high eosinophilia; fever is not characteristic, and enlargement of the spleen is not present. The wheezing in asthma is usually higher pitched.

Loeffler's syndrome has a transient but more solid infiltration of the lungs as shown by x-ray films; white cells are usually up to about 15,000, and eosinophilia is marked. The consolidation usually clears in three to eight days. Hansen-Pruss and Goodman<sup>45</sup> report migratory pulmonary consolidation occurring in six allergic individuals. They prefer the term "allergic pulmonary consolidation" to "Loeffler's syndrome." In their cases, the eosinophilia persisted after the asthma and x-ray evidence of consolidation had disappeared. Sulfonamides were of no benefit. No fatalities have been reported. Jones and Souders<sup>56</sup> made fluoroscopic examinations of the chest of 6,283 discharged soldiers; abnormalities were found in fifty-five cases, thirteen of which were diagnosed as Loeffler's syndrome. Pirkle and Davin's patient<sup>75</sup> showed consolidations which continued to migrate for eight months. Lowe's paper<sup>64</sup> deals with eosinophilia found in servicemen who have become worm-infested while in the tropics.

### MILITARY ASPECTS

All medical officers agree that asthmatic individuals do poorly in the Service. They urge civilian physicians to send notes to the induction boards to keep their asthmatic patients out of the Service. Gold and Bazemore<sup>39</sup>, from Camp Blanding, Florida, have made special allergy studies prior to induction on all individuals with a history of allergy. The local induction station referred 143 persons who gave a history of asthma. Of these, 132 were diagnosed bronchial asthma, and 42.4 per cent were recommended to be rejected from military service. It is much better to reject these men at once than to force them from their civilian pursuits, as most will develop more attacks of asthma in the Service, be hospitalized and finally discharged. Edwards<sup>28</sup>, from the Letterman General Hospital, San Francisco, California, has attempted to prove the presence or absence of allergy in selectees and in candidates for commissions. He makes scratch tests first, then intracutaneous, if necessary. He uses extracts of mixed trees, grasses, fall pollens, timothy, ragweeds, epidermals, some inhalants (flaxseed, cottonseed, pyrethrum, and orris root), mold mixtures, and house dust. He omits food tests as unreliable in many cases and therefore unsuitable for mass testing. This procedure is a step in the right direction.

Although patients with asthma of any but the mildest degree are not supposed to be in the armed forces, the fact is that thousands of them are in the Service, are taking up hospital beds, are receiving care in clinics, and are being discharged, some with pensions. During 1942, Gold and Bazemore<sup>39</sup> report that 399 allergic patients were admitted to their hospital and 911 to their outpatient clinic. Bronchial asthma was the diagnosis in 51 per cent of the cases, a rate of 4.8 per 1,000 soldiers. Of those hospitalized, 24 per cent of the asthmatic patients were discharged from service, 58 per cent returned to full duty, the rest to limited duty. It is interesting to note that 65 per cent of those discharged had less than six months' service prior to discharge, and 21 per cent had less than thirty days of service.

Alford<sup>2</sup>, from the Percy Jones Hospital, Battle Creek, Michigan, summarized his first 100 cases of asthma in soldiers, and concludes:

1. Men with active bronchial asthma should not be inducted.
2. Soldiers with bronchial asthma may be placed on nonstrenuous duty if:  
(a) their attacks are due to a single sensitivity for which rapid, adequate treatment is available

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- (b) attacks are mild and infrequent, not preventing light duties
- (c) the initial attack occurred overseas
- (d) the attack in the Army was the first one since childhood.

Alford also found that in soldiers whose first attack occurred overseas, a positive family history was only found in 21 per cent, as compared to 65 per cent in those whose asthma was present since childhood. Alford also made skin tests with extracts prepared from dust secured from barracks bags which had been overseas and found the nitrogen content of overseas dust was twenty times as strong as his stock United States dust. One patient had a severe attack of asthma after 0.10 c.c. of this overseas dust extract, and asthma was also induced by inhalation. Molds, dust, and dampness seem to be the important factors, especially in the South Pacific.

Hampton and Rand<sup>43</sup> report from the Allergy Section and Clinic, A.A.F. Regional Hospital, San Antonio, Texas, Aviation Cadet Center, from August 1, 1943, to August 1, 1944. During the year, 8,409 visits were made by Air Force personnel to the Allergy Clinic. There were 1,541 new patients, of whom 921 had respiratory allergy (hay fever, vasomotor rhinitis and asthma). Of 1,191 men who were discharged from service, 106 (8.9 per cent) had allergic diseases; eighty-six of these had bronchial asthma. Respiratory infections, both acute and chronic, were frequent and important complications, and occurred in 191 of 286 cases of asthma.

French and Halpin<sup>47</sup>, from the Fourth Service Command, Atlanta, Georgia, continue their reports, but, unfortunately, their team has been dissolved. They gave four courses of instruction to 180 medical officers, and they treated 32,046 allergic soldiers. They used standardized allergenic extracts prepared by their own laboratory; manufacture of these extracts has been discontinued. They supervised eighty-nine allergy clinics in this command. French and Halpin report as follows: 9,591 cases of bronchial asthma, of which 946 were seasonal; 1,384 were associated with hay fever, and 7,261 were perennial. Asthmatic soldiers occupied many of the hospital beds, 5,447 of a total of 8,139 beds filled by allergic individuals, including sufferers from poison ivy. The Certificate of Disability Discharge was given to 3,231 asthmatic soldiers.

Discussing this paper, Leider<sup>62</sup> gives 1943 statistics from the Walter Reed Hospital. Asthma occurred in both white and colored patients, and both "extrinsic" and "intrinsic" cases occurred. Asthma occurred prior to military service in 75 per cent of the cases, and during military service in 25 per cent. There were 186 asthmatic soldiers; of these, twenty-nine (15 per cent) had their first attack overseas, fifteen in Porto Rico and seven in Panama. Another 71, when overseas, had exacerbations of pre-existing asthma; in this group, England, with twenty-four cases and with a damp climate, led all other countries. Dampness is a definite factor in England and in the tropics. After these overseas asthmatic soldiers returned to the zone of the interior, forty-two of the 100 remained free from asthma, thirty-five had mild and twenty-one moderate symptoms, and two had severe attacks. Of the total 186 cases, ninety-one were returned to limited duty and ninety-four were discharged from the Service.

Shahon<sup>61</sup> discusses the difficulties encountered by the induction board physician. He points out:

1. If the examiner's physical examination of the soldier is negative, there is no history of allergy in the soldier or in his family, and skin tests, if done, are also negative, then allergic disease was not present at the time of induction. If this soldier should later develop an allergic disease, the condition has developed during service, and if discharged he is entitled to full benefits. It is possible that factors like overexertion, worry, exposure to excessive cold or heat, emotional strain, et cetera, may precipitate symptoms.

2. If the allergic condition was mild at the time of induction and later became so severe as to cause separation from the Service, the disease was undoubtedly aggravated by service. As regards rating for pensions, Shahon points out that, as

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with other conditions, allergic diseases are rated in terms of severity. For example, asthma is rated:

- (a) asthma, mild—symptoms in attacks at widely separated intervals; no complications. Rating 0 or no per cent.
- (b) asthma, moderate—symptoms rather frequent (ten to fourteen-day intervals), with slight to moderate emphysema, with moderate dyspnea between attacks. Rating 30 per cent.
- (c) asthma, severe—frequent attacks, with moderate to severe dyspnea with emphysema, and also if heart action embarrassed. Rating 50 per cent.
- (d) If, with above symptoms, soldier also has dyspnea at rest with cyanosis and total disability. Rating 100 per cent.

### ETIOLOGY OF ASTHMA

Allergy to molds again is a subject for discussion. Despite many earnest studies, it is still apparent that there are some who are over-enthusiastic about the role of molds in causing asthma and rhinitis, and that others believe that molds are of little importance. The majority of investigators, however, know that molds are important, but we are still groping in many aspects of the question. Those who rely on scratch tests are convinced (this author is among this group) that positive scratch tests plus a good history for mold etiology means clinical allergy to these molds. But reliance on positive intradermal tests for molds is not nearly as accurate. This is shown by the somewhat pessimistic attitude of Prince, Morrow, and their coworkers who realize that they have lost a good part of the antigenicity in their method of preparing mold extracts. Realizing this, they are earnestly correcting their technique. Prince and Morrow<sup>50</sup> describe their methods of preparing mold extracts. Both spores and mycelia of *alternaria* and *aspergilli* are thoroughly broken up by the ball mill process. Defatting is not important. Prince<sup>79</sup> tested nine normal individuals with extracts of *alternaria* as well as with saline washings from pellicles and the broth from which the pellicles are grown, and found that these caused no skin irritation. But when pellicles in saline solution are washed prior to extraction, some of the positive-skin-testing quality is lost, as shown by tests on *alternaria*-sensitive patients.

Zink<sup>118</sup>, in another study in this series, concludes that:

1. Air-borne molds are clinically important in 25.5 per cent of 705 tested patients
2. *Alternaria* are the most important molds, with *helminthosporium* and *hormodendrum* lesser factors
3. *Aspergilli* and *penicillia* are of little clinical importance

Selle<sup>90</sup> was unable to demonstrate histamine or a histamine-like substance in the washings of *Aspergillus niger* or *Alternaria tenuis*, or in the broth on which these molds were cultured. Nor could he detect histamine-like substances in concentrated extracts of these molds which were used for skin tests. Figley and his co-workers<sup>35</sup> made intracutaneous tests on fifteen patients with clinical respiratory allergy to *Alternaria tenuis*. There were twenty-four control patients. *Aspergillus niger* was also tested. They found that the experimental extracts were about as active as extracts of the same fungi prepared by the usual methods; variations in technique of preparation were not important. Passarelli and his associates<sup>73</sup> have shown that molds are important allergens in Rio de Janeiro. Studies made from May 11 to September 4, 1943, revealed that the most common molds are *penicillium*, *hormodendrum*, and *aspergillus*; *alternaria* were rarely found.

New allergens have been reported. Oliveira Lima<sup>63</sup> described a patient with a positive family history of allergy who developed rhinitis and asthma five months after beginning the regular use of an insect powder containing timbó. Contact dermatitis developed at the same time. Timbó (*Lonchocarpus*) and Derris (*cubé*) are both plants of the *Leguminosae* family and are used as insecticides. In this patient,

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scratch and passive transfer tests were positive for both plants. Patch tests were positive with the resinous constituents of timbó. Incomplete animal experiments indicate some cross reaction between the two plants. Sterling and Hollander<sup>95</sup> discuss a woman whose home, especially her bedroom, contained a great number of plants, and who suffered from bronchial asthma for fifteen years. Tests for the usual allergens were negative, but she gave two plus reactions to the following molds found in the soil: *helminthosporium*, *rhizopus*, and *aspergillus flavus* and *nidulans*. When the plants were removed from her house, she improved remarkably. Re-exposure to the plants was followed by asthma. Skin tests were strongly positive both for extracts made from the leaves of an *Aspidistra* plant and from the soil of the plant which contained hyperhumas fertilizer. Passive transfer tests were doubtful. Injections of both extracts have been given, and the patient has been symptom-free.

Cotter's patient<sup>21</sup> was shown to be allergic to aluminum dust which he inhaled when he bored holes into aluminum plates. Recovery followed removal from this dust, and exposure again brought on asthma. No skin tests were made. Toomey and Petersilge<sup>102</sup> describe a type of noninfectious dust bronchitis previously observed in the Dust Bowl area; similar symptoms occurred in institutionalized children who inhaled finely pulverized dust from a nearby playground. To complicate an already overcomplicated situation, Hooker<sup>58</sup> has shown that there is a qualitative difference among dog danders, depending on the breed of the dog! Cross-neutralization occurs between some breeds but not between others. It is therefore almost impossible to obtain a representative multivalent extract of dog dander. This may explain why skin reactions to dog hair extracts are almost always weaker than extracts of cat hair or horse dander. We should test patients with extracts made from the dander of their own dogs as well as with mixed dog hair extract.

Foods also cause symptoms, and Rinkel<sup>87</sup> states that the following events indicate that foods are the cause of asthma:

1. Production of large quantities of mucus
2. Acute attacks lasting two to five days, without essential changes in environmental factors
3. With the same environment, the occurrence of acute attacks in the middle of one night a week
4. Asthma only in the mornings and up to noon, then none the rest of the day
5. Asthma occurring each day about 4:00 to 5:30 P.M., not related to, or affected by, other inhalant or environmental factors.

This is typical, says Rinkel, of a food eaten both at breakfast and lunch. Nasal symptoms may accompany or replace asthma. Horesh<sup>54</sup> reports the case of a child who developed severe asthma both from eating cooked white potatoes and from the odor of potato, cooked or raw. Cooking odors are fairly frequent causes of asthma and rhinitis. Scratch tests were positive for potato and other foods and inhalants. Coca<sup>17</sup> again discusses his theory of "nonreaginic food allergy," as determined by an increase in pulse rate. This work may be important but needs confirmation.

A number of articles on miscellaneous causes of asthma have appeared. Thus Earle<sup>27</sup> describes the case of a sailor from the British West Indies who developed his first and only attack on board ship; the asthma disappeared when he vomited material containing three live ascaris worms. The stools were negative for parasites, and the personal and family history were negative for allergy. Skin tests, both scratch and intradermal, were positive for an aqueous extract of preserved ascaris. No further workup was possible, and, unfortunately, the sailor was killed in action a month later.

Another case of sensitization to thiamine hydrochloride comes from Stein and Morgenstern.<sup>94</sup> Their patient, addicted to the use of alcohol, previously had injections of thiamine. The latest series was given at regular intervals, and each

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was followed by severe local pruritus and urticaria. Fifteen minutes after the eighth injection, generalized pruritus developed, together with asthma, shock and coma. Gradual improvement followed the administration of epinephrin and caffeine, although asthma persisted. Intracutaneous tests with thiamine led to a wheal and itching which persisted for six hours. Passive transfer was not done.

An important article comes from Randolph and Rawling.<sup>86</sup> Status asthmaticus developed in a patient on the seventh day of the nasal use of a solution containing sulfathiazole. Personal and family history were negative for allergy. One week after this patient was symptom free, a trial feeding of sulfathiazole caused a typical paroxysm of asthma, together with decreased vital capacity. Another patient, already allergic as shown by the history of atopic dermatitis, asthma and allergic rhinitis, developed asthma after the first dose of a second course of sulfathiazole treatment. In both cases, there was an increase in the percentage of eosinophiles in the blood in twenty-four to forty-eight hours after the sulfathiazole was given.

An interesting article from Deissler<sup>24</sup> would become practical only if gas warfare is resumed. He points out that any sort of respiratory irritant, e.g., various fumes, chemicals and smokes, tends to incite or aggravate attacks of asthma. Poison gases are especially potent in this regard. Therefore, an asthmatic patient should have priority in obtaining a gas mask. He should also:

1. Try on his mask frequently to eliminate psychic factors
2. Take epinephrin or epinephrin in oil and some ephedrin at the onset of the gas attack
3. Wear an identifying tag specifying that he has asthma, and, if necessary, that he should receive aminophyllin or epinephrin but no morphine or other opiates
4. He must not inhale 1:100 epinephrin during an attack for fear of inhaling the poison gas.

These precautionary measures may seem absurd, but as one who has gone through "gas" attacks and has worn a gas mask, they may become important.

Two papers concern the relationship of asthma and the weather. Feige and Rosenbaum<sup>31</sup>, from Tel-Aviv, Palestine, made meteorologic studies on three isolated dates when many children with chronic asthma developed severe attacks. There were no special changes in weather conditions on these three dates, although the authors point out that the asthma may have been due to sudden appearance of pollens in the air. Petersen and Vaughn<sup>74</sup>, in a scholarly exposition, conclude that "The inference is obvious that the clinician, while properly interested in the allergic background of the clinical symptoms, should by no means neglect the other environmental forces which are of significance not only for the allergic patient but for other individuals as well. Recognition of the basic organic rhythm, with its periods of increased or decreased susceptibility to attack, should, under all conditions, prove useful in the evaluation of the symptoms and therapy, as well as the prognosis." They strongly support Hilding's view<sup>51</sup> that, as a result of the local changes in the smaller bronchi, the ciliary action is lost, and the difficulty of removal of secretion is aggravated because the mucus remains attached over large areas to the cells which produce it, thus anchoring the mass to the wall. When the air passages have become sufficiently filled, the patient dies of asphyxia.

Psychosomatic allergy continues to draw attention. Mayer<sup>66</sup> believes that asthma is not a disease but a symptom-complex, and may be due to many causes; e.g. allergy, heart disease or any other cause of bronchial obstruction. His patient had several attacks of asthma which were precipitated by psychic stimuli, and the author therefore diagnosed the condition as "psychogenic asthma" and says the psychosomatic approach offers the best results in the treatment of asthma. (This paper, to me, is very poor, as it sees only the psychic aspects of asthma which we all grant are important but which are of little importance when the exciting organic cause, e.g., dog hair or egg white, is avoided). Another almost absurd article comes

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from a nurse, S. Lane<sup>59</sup>, who writes about her own asthma. She accuses physicians: "I have never heard one of them mention the possibility of emotional factors causing asthma. They always seem to think that it can arise only on an organic basis." She discusses her own emotions as regards asthma; she has crying spells which she believes are substitutes for asthmatic attacks.

Brown and Goitein<sup>13</sup> state that "most investigators are agreed that a complex series of factors are involved in the perpetuation of the disorder and the initiation of accentuation and amelioration of attacks." They believe that sex is closely related to allergy and state that "sensitivity is displaced repressed sexuality." (It is hard to believe this; how can sex operate, for example, in a child whose asthma begins in infancy?)

Rubin and Moses<sup>88</sup> studied fifty-four asthmatic males by electroencephalograms and personality data. The former indicate a definite relationship between bronchial asthma and a dominant alpha record, i.e., about three times as many dominant alpha records were found in asthmatic as in normal persons. Dominant alpha records have been correlated with passive receptive type of persons. The author's own personality data indicate, in general, that there is a single family definite personality constellation. Asthmatic patients are fundamentally in the passive dependent group, and are children of overprotective dominating mothers. They have not cared for, striven for, or gained any marked degree of independence in life, and they continue to seek care and protection from their environments. Zeller and Edlin<sup>112</sup> studied 372 insane individuals by means of skin tests, histories from relatives and friends, and by watching for allergic symptoms, e.g., hay fever. By this systematic allergy survey, they proved that there is just as much allergic disease in the insane as in the sane. The reason one does not find symptoms in the insane is that he does not complain. Only the severe instances of allergy come to the attention of the medical attendants. This paper is in direct opposition to that of Leavitt<sup>61</sup>, who studied (but not by skin tests, merely by complaints of the patients and the observations of the medical staff) 11,647 patients afflicted by functional psychoses. He found only ten cases of bronchial asthma in this group, an incidence only about 5 per cent of that found in the general population. Leavitt did not find a single case of asthma in 5,000 mental defective and epileptic inmates of a state institution.

## PATHOLOGY OF ASTHMA

Four papers on the pathological aspects of asthma need comment. Rackemann<sup>81</sup> discussing death from asthma, concludes that death is due to the development of obstructing plugs of tough, sticky mucus. The "typical" asthmatic lung was present in twenty-seven of his fifty cases in which death was due to asthma itself: voluminous distended lungs of bluish gray color; cut section reveals that the bronchi, especially those of medium or small size, are partially or completely occluded by plugs. He reports 55 other cases in the literature in which the "typical" asthmatic lungs were found, i.e., cases in which the clinical history and the mode of death are characteristic of bronchial asthma, in which autopsy reveals voluminous lungs and bronchial plugs, and in which there was no gross evidence of any other cause of death. In Rackemann's series, a total of 82 patients died because of asthma; most deaths occurred in those whose asthma began after the age of forty-five, but typical symptoms and pathological changes can also occur in younger persons.

Since this article was written, Unger, in his book on "Bronchial Asthma"<sup>105</sup>, just published, reports four more cases in which death was due to asthma; autopsies showed "typical" asthmatic lungs.

Hagen<sup>42</sup> studied the cervical ganglia removed from seven patients because of severe asthma. Sections revealed pathological changes in almost all ganglia, with disharmony of processes with hypertrophic glomerulus-like ball formation. Vacuolation and granular degeneration were frequent in the body ganglion and the processes,

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and there was an increased number of multinuclear ganglion cells. These changes may perhaps explain some of the secondary symptoms of bronchial asthma. Brandes, Cooke and Osborne<sup>10</sup> report an unusual case. A thirty-one-year-old man had recurrent attacks of dyspnea, without fever, for three successive winters, and dyspnea persisted during the year preceding death from asphyxia. Allergy studies were negative. Autopsy revealed emphysema, aberrant growth of bronchial lymphoid follicles, sclerosis of the small branches of the pulmonary arteries and arterioles, and cor pulmonale.

Harkavy<sup>46</sup>, in a discussion of fifteen cases of asthma, including four that came to autopsy, concludes that:

1. Bronchial asthma is an expression of hyperergic vascular response, reversible or irreversible
2. The tissue changes do not represent disease entities but rather qualitative and quantitative degrees of hyperergic and anergic response, and
3. The syndromes dependent on such vascular reaction in the myocardium, pericardium or other serous membrane, and expressed as cardiac insufficiency, constrictive pericarditis, or polyserositis, may therefore be attributed to an allergic mechanism.

### SYMPTOMATOLOGY OF ASTHMA

Thomas and Taylor<sup>100</sup> define "allergic bronchitis" as "an allergic reaction to one or more specific sensitizing substances in a susceptible individual, and is characterized by a chronic, recurring, or paroxysmal cough. In most instances, it is not associated with dyspnea, and it usually occurs in the absence of any upper respiratory tract infection or intrathoracic pathologic condition which otherwise might account for the bronchitis." Allergic bronchitis occurred in 12 per cent of all patients admitted to the allergy department of the Cleveland Clinic. Almost all cases also had an allergic rhinitis; onset in 46 per cent followed some acute respiratory infection; hereditary influences were similar to those found in bronchial asthma; physical and x-ray examinations were not conclusive; skin tests were frequently positive. The treatment was that used for asthma and gave excellent results, with only 15 per cent failures. Unfortunately, no sputum tests for eosinophilia were included. This condition is important because adequate and early diagnosis and treatment will usually prevent the onset of asthma.

Classifications of asthma have been proposed by Cohen<sup>18</sup> and Coke<sup>19</sup>. Cohen stresses the elaboration of histamine or an H-substance by the cells when excited by extrinsic factors; symptoms are then due to the action of this substance on the cells of the bronchial tree. He classifies cases into extrinsic, intrinsic, and combined. Coke, from England, again classifies asthma into: (1) allergic; (2) microbic, and (3) aspirin-sensitive or mixed groups. These groups may overlap. Autogenous bacteriophages have given good results in the infectious cases. Coke complains that the allergic cases are being neglected by British physicians, and warns that, if the neglect continues, the municipal authorities will probably run the asthma clinics with the assistance of physicians cognizant of the proper care of asthma.

Swineford and Weaver<sup>97</sup> show that there has been too much emphasis on skin-testing and not enough on history-taking. They present a nice outline for taking histories, and criticize many books on allergy because they do not detail important questions to be asked patients. Skin tests are nicely evaluated by Steele<sup>98</sup>, who points out once again the proper technique, and stresses the fact that skin tests are only a valuable adjunct to the history and clinical findings and should not be given undue importance. He correctly warns against the use of combined extracts for testing. Stoesser<sup>96</sup>, working with children, uses the puncture method on the back; positive tests for foods are of the greatest value in infants, inhalants in the pre-school age, and pollens up to and through puberty. Inhalants are much more important than foods, even in children.

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Randolph<sup>85</sup> describes a new method of counting white cells. His diluting fluid contains phloxine and methylene blue in equal parts of propylene glycol and water. The eosinophiles and other white cells are counted directly in the blood chamber, and the eosinophiles are easily seen. It is therefore not necessary to make the usual stained differential smears.

Papers on varied subjects have also appeared. Herrioz Ballester<sup>5</sup> discusses impaired nutrition as an allergic manifestation. It is especially frequent in asthmatic children, one-third of whom are underweight (15 to 50 per cent); thoracic deformities are common. Proper anti-allergic treatment markedly improves nutrition. Thomas and House<sup>99</sup> report a case of status asthmaticus complicated by drug allergy, sinus infection, and dermatitis medicamentosa due to neosarsphenamine. Edema of the legs also occurred when sulfadiazine was given for fever associated with the asthma. Rackemann<sup>82</sup> discusses new theories concerning patients whose asthma starts late in life and progresses despite all treatment. These are "intrinsic" in that no evident allergen has been discovered, yet the blood eosinophilia is high, 13 to 20 per cent in one case. He believes that sinus surgery rarely cures, and he suggests operation only when the condition of the sinuses is so bad that intervention is indicated without regard to the asthma. He is intrigued by the relationship of asthma to the adrenal gland, especially the cortex, but, unfortunately, has nothing new to offer in the line of treatment.

Tocker and Davidson<sup>101</sup> reviewed 386 patients at the Sea View Hospital for Tuberculosis; 3.1 per cent of the patients also had bronchial asthma; (this percentage seems high). They point out that skin reactions to allergens are weaker and more delayed than in non-tuberculous allergic individuals. They were very careful in differentiating true bronchial asthma in these tuberculous patients from the "asthmatic" breathing caused by tuberculous bronchopulmonary pathology. Interesting: asthmatic symptoms tend to improve with activity of the tuberculosis and to recur with healing—another probable instance of nonspecific action. Asthmatic attacks should be combatted because they aggravate the tuberculous infection, and artificial pneumothorax is apt to cause exceptional dyspnea in patients with asthma and tuberculosis.

Pulmonary complications, especially atelectasis and spontaneous pneumothorax, are not rare in asthma; subcutaneous emphysema is less common. Atelectasis probably occurs more frequently than we can prove, and Cole, Nalls, and Buis<sup>20</sup> report four more cases of asthmatic atelectasis which simulated pneumonia. Diagnosis was aided by the x-ray and by bronchoscopy and bronchogram. Sulfonamides were not helpful, but when the obstruction of the bronchus, cause of the atelectasis, was removed by coughing up or bronchoscopically removing the plugs, the symptoms rapidly abated. Fever, pain in the side, dyspnea, and nonproductive cough are the chief complaints.

Trowbridge<sup>103</sup> discusses spontaneous pneumothorax in asthma and advises against removal of air. Engelhardt and Derbes<sup>30</sup> review twenty cases in the literature, in only two of which autopsy was done; their own patient had asthma, developed spontaneous pneumothorax, and died suddenly. Autopsy confirmed the diagnosis. They urge against thoracocentesis although they repeatedly tapped their patient. They believe that the air escapes into the pleural cavity by rupture of a valve vesicle. Field's patient<sup>33</sup> was a girl of four who eventually recovered despite the fact that she had bronchial asthma, subcutaneous emphysema with massive collapse of the left lung, and spontaneous pneumothorax of the right chest. Fortunately for the patient, else she could hardly have survived, there was an interval of 15 days between the asthma and the initial subcutaneous emphysema with collapse of the left lower lobe, and the second episode characterized by asthma, collapse of the left upper lobe and spontaneous pneumothorax on the right side. This combination is very rare. Francis<sup>36</sup> adds two cases in which subcutaneous emphysema occurred

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during acute asthma. These cases are dramatic but not serious. The rupture occurred during a severe paroxysm, with resultant dyspnea, cyanosis, and swelling of the neck and adjacent parts. Crepitus was prominent, and the air was absorbed in seven and ten days, respectively.

Day<sup>23</sup> says that "diaphragmatic dyspnea" is the most common disorder of the respiratory system in the British army. The cause is faulty diaphragmatic function, and appears late in military training, with physical signs suggestive of emphysema. Fluoroscopic examination reveals slight, absent, or paradoxical excursion. Breathing exercises are indicated. There are two recent articles on paroxysmal cardiac dyspnea (cardiac asthma). Karmally<sup>58</sup> gives a nice differential diagnosis from bronchial asthma. For attacks of cardiac asthma, he advises morphine, venesection and rest; constriction of the veins in both arms and legs may help, and oxygen may also be necessary. Harrison<sup>48</sup> agrees with this therapy.

### TREATMENT OF ASTHMA

Many articles on various phases of treatment have recently been published. Most offer refinements, and many are surveys of methods already in use.

Prevention of asthma is very important, and we are on the threshold of a campaign to prevent or at least to lessen the incidence of asthma in children. Much can also be done to prevent asthma in adults. Gray and Albert<sup>41</sup> discuss eight individuals with pre-asthmatic symptoms, e.g., nasal congestion, sneezing, rhinorrhea, cough, or dyspnea. Asthma developed only when exposed to occupational dusts, e.g., feathers, furs and fur dyes, flour, cadmium fumes (platers), and insecticides. Removal brought relief. Allergic patients should be excluded from occupations with such dusts. Derbes and Winsor<sup>26</sup> add laboratory workers, food handlers, jewelers, beauticians, pharmacists, and chemists to the list of occupational allergic hazards. Although change of occupation is the best therapy, many workers will not or cannot do this; it is therefore necessary to take all possible measures for removing or lessening the amount of such dusts; hyposensitization with environmental dust extracts may be very beneficial. Many of their patients were over forty and might have been wrongly classified as "intrinsic," with resultant neglect. The control of nonoccupational allergens is also important.

Inhalation therapy has again been stressed. Barach<sup>6</sup> has outlined a long and involved series of procedures for status asthmaticus.

He advises:

- (a) Inhalation of helium-oxygen mixtures or oxygen alone
- (b) Aminophyllin intravenously, orally, and by rectal suppositories
- (c) Potassium iodide
- (d) Neosynephrin inhalations by nebulizer
- (e) Sedation, preferably by sodium luminal

When attacks are severe, he uses:

- (f) Ether, per rectum
- or
- (g) Intravenous injections of typhoid vaccine

He also advises demerol or dilaudid. (Demerol is often efficient and rarely harmful, but dilaudid is an opiate and as dangerous as morphine, and should not be used in any attack of asthma). Barach continues these procedures even after improvement has set in—"repeated bronchial relaxation."

Weisser<sup>110</sup> has a nice paper on chronic asthma. Treatment consisted of massage, rhythmic compression of the chest, resounding breathing exercises, and regulated gymnastics, e.g., boxing, jujitsu, and calisthenics. These procedures were given daily for many months, even years. Tolerance for exercise was gradually increased, and dyspnea due to exertion was decreased because the patient's vital capacity increased as his expiratory time diminished. Results: thirteen of twenty-nine children free from attacks for three and one-half years, ten improved, six no

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relief. Of ten adults, one free from attacks, five improved, four not improved. The procedures are therefore especially valuable in chronic asthma in children. Gay<sup>38</sup> also advocates chest massage in such cases; his patients blow air from one two-gallon bottle to another and then back again. This therapy seems very logical and should be more widely adopted.

Vaccine therapy is described by Prince<sup>78</sup>, Boyd<sup>9</sup>, and Brunk.<sup>15</sup> Prince, in discussing asthma complicated by respiratory infection, stresses the importance of examining sputa for bacteria and for the type of cells. Chemotherapy is excellent in many cases, especially if pneumomocci are present. He uses autogenous and stock vaccines, depending on the number of specific bacteria. If stock vaccines give good results they are continued. If not, autogenous vaccines are used. He rightly frowns on radical sinus surgery unless frankly purulent sinusitis is present. Boyd advocates injections of B. H. (Hoffman's bacillus) vaccine in various allergic disorders in which accepted methods of treatment have failed. He begins with 0.10 c.c. and increases cautiously, with due regard for local or systemic reactions, up to 1.0 c.c., and keeps up this dosage for months or years. Brunk, in a study of 500 private patients, determines the antigen-producing properties of organisms recovered from foci of infection. He uses about 35 antigens, including the colon bacillus, micrococcus catarrhalis and the ordinary strains of staphylococci and streptococci. The tests also show the specific organism to which the patient is sensitive. Then cultures of all available excretions, including the urine and stools, are tested for the responsible antigen. Once the offending organism and focus of infection are determined, the treatment is primarily surgical, i.e., removal of the focus. Vaccines made from the specific organisms are very potent, and must be given in small doses. Deficient complement in the patient's blood stream indicates a bad prognosis and constitutes a definite contraindication to surgical interference. The methods of Boyd and Brunk should be repeated by other investigators.

Drug therapy continues to draw attention. Brown<sup>12</sup> gives a list of more than 200 advertised commercial products, most of which are not Council Accepted. Some are ethical, others not. The composition of each is noted, and is very useful. Brown suggests the use of the best possible medication at the lowest possible price. Another list of patent medicines used in asthma is also in Unger's new book on Bronchial Asthma.<sup>105</sup>

Brown, Wilder and Schwartz<sup>14</sup> studied local reactions in rats and rabbits from intramuscular injections of corn, cottonseed, sesame and peanut oils. Corn oil was the least viscid, and remained fluid to minus 15° C. Chemical agents used as preservatives are irritating. Corn and sesame oils produced the least amount of local reaction in the muscles of these animals, peanut oil the most marked. Harris and David<sup>47</sup> gave 50 mg. ephedrin sulfate daily to seven normal individuals for three to four weeks. Within three weeks, there was an average rise of one-half million red blood corpuscles and a corresponding increase in hemoglobin. The white cells were not changed. After four weeks of therapy, the red cells and hemoglobin usually returned to normal even though the use of ephedrin was continued. Therefore, the prolonged use of ephedrin is not harmful to the blood.

Demerol, the new analgesic and substitute for morphine, is discussed by Yonkman, Noth and Hecht, and by Noth, Hecht and Yonkman.<sup>11</sup> Pharmacologically, demerol resembles atropine in its anticholinergic action with production of mydriasis, suppression of saliva, and antivagal action on the heart, bronchi and intestines. It resembles papaverine in its spasmolytic action, directly relaxing the musculature of the bronchi, intestines, uterus, and blood vessels. It resembles morphine in its analgesic, sedative, and euphoric effects. It is a relatively safe drug. Clinically, it is given orally or intramuscularly in doses of 75 to 100 mg. and may be repeated one to eight times daily. For children, dosages of 10 to 75 mg. are recommended. If given intravenously, demerol should be diluted and injected slowly. The results are often

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good. In one patient, however, oral administration was followed on two occasions by severe vasomotor collapse, bronchospasm, nausea and vomiting. Addiction is not as pronounced as with opiates.

Hansel<sup>64</sup> gave  $\frac{3}{4}$  grain nethamine hydrochloride and 2 grains of theophylline isobutanolamine to 250 patients over a period of three years. The symptoms associated with allergic rhinitis and asthma were satisfactorily lessened. Nethamine has ephedrine effects without the unpleasant side effects. The other drug is a xanthine compound, similar to aminophyllin but more soluble and less toxic. The combination was made up in scored tablets, and the average optimum adult dose was  $\frac{1}{2}$  tablet; in children  $\frac{1}{4}$  tablet. The combination can also be used intravenously, intramuscularly, or in rectal suppositories.

Merrill<sup>67</sup> reported three deaths in "asthmatic" patients during or shortly after intravenous injections of 0.25 gm. of aminophyllin. One might conclude that the drug is dangerous in bronchial asthma. Unger<sup>106</sup> analyzed these cases, and showed that all three were suffering from severe cardiovascular disorders, and suggested that the drug may be dangerous when given intravenously in cardiac diseases. In uncomplicated bronchial asthma, however, the slow intravenous injection of aminophyllin is highly beneficial and not at all dangerous. An occasional episode of nausea may result.

A very interesting paper comes from India. Chatterjee<sup>16</sup> gave adrenalin and atropine but was unable to control asthma in a twenty-eight-year-old woman who had had asthma since the age of five.

"She was tired and exhausted, groaning and moaning at each breath, appealing to humanity for help, seeking the mercy of God, begging the doctor for relief or even welcoming death. I gave her the same injections as before but moved too much by patient's misery, I was determined to give her some relief and rest. I gave morphine gr. 1/6 with a clean conscience. The result was marvelous. Within two minutes the patient felt relieved, thanked me for saving her life and gave me my dues and all previous dues up to date overwhelmed with gratitude. She took a little barley and asked her mother to clean the bed at once for she wanted to sleep. I left the place at 9:30 p.m. I was called again at 10 p.m. I found her pulseless with respiration very slow, 7 per minute. I declared the case as hopeless. The patient died at about 11 p.m."

The doctor concludes: Don't give morphine in asthma. This dramatic description needs no comment.

Reactions continue to occur. Applebaum<sup>4</sup> describes cerebrovascular accidents in two young males who had been given their first injections of 0.50 c.c. of 1:1,000 epinephrin for asthma. The first man became restless and apprehensive in a few minutes; speech difficulty and right hemiplegia and right facial paralysis followed. There was moderate vasoconstriction of the retinal vessels. The findings began to subside in a few hours, and in five weeks, the soldier was normal, except for a slight facial palsy. The other patient quickly developed headache, nervousness, palpitation, mental symptoms, and paralysis of the left arm and leg and the left side of the face. This episode was completely gone in two hours. A few similar cases have been previously reported. Deissler's patient<sup>25</sup> had asthma and hay fever and also a well-compensated rheumatic double mitral heart condition. Through an error in dosages and after an interval of thirty-four days from her previous injection, she received an increase of 20 per cent of pollen extract. She remained in the office 20 minutes, and revealed the usual local reaction. On the way home she coughed up thin watery pinkish fluid and became dyspneic and cyanotic. Her blood pressure dropped to 80/50, with pulse 140 and many fine moist râles through both lungs. The usual treatment for allergic reactions (cuff, epinephrin and intravenous aminophyllin) gave no relief, but morphine caused quick relaxation. This was not the usual allergic reaction, but was an instance of acute pulmonary edema following

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an overdose of antigen. Unfortunately, the patient's cardiac reserve has not completely returned to normal, and she now takes 0.1 gm. digitalis daily. Biglers<sup>8</sup> has an interesting paper on allergic reactions resulting from injections of toxoids; fortunately, no deaths have as yet been reported. The peptone in the mixture seems to be the responsible agent.

Ethylene disulfonate is still a disputed remedy. Wasson<sup>108</sup> used it with good results in children with asthma; control cases were also studied. Bartlett<sup>7</sup> tried it in 247 consecutive allergic conditions in children, with satisfactory results in 86.64 per cent. The average number of 2.0 c.c. injections per patient was 1.41. Dr. Chauncy Leake, Professor of Pharmacology and Dean of Texas Medical School<sup>60</sup> reports that, from a scientific point of view, the claims of the manufacturer could not be duplicated. He believes the drug "will eventually rest in the limbo of forgotten therapeutic agents."

Tainter and his associates<sup>98</sup> state that ethylnorsuprarenin is useful in the treatment of asthma and possibly preferable to epinephrin for those patients in whom the latter drug gives undesirable side effects. The drug acts like epinephrin as a sympathomimetic, but does not raise blood pressure, and in animals it is 1/120 as toxic as epinephrin. Confirmation by other workers is urged as such a drug is desirable.

Prickman and Gelbach<sup>76</sup> report that postoperative pulmonary complications occurred in only 15 per cent of 142 asthmatic patients who experienced major surgical procedures. Pneumonia occurred in six cases, atelectasis in six, and severe asthma in four. The incidence was twice as high after operations in the upper abdomen as in the lower. Two deaths occurred, a mortality rate of 1.4 per cent. Patients with infectious asthma were more apt to develop pneumonia, and spinal or intravenous anesthesia was preferred. In fifty-eight patients who received ether, ten developed pulmonary complications. The usual allergy management was given, and the authors suggest postponement until warm weather, if possible, of operations in patients who have infectious types of asthma.

Nonspecific treatment is further illustrated by three other articles. Fiessinger and his associates<sup>34</sup> had a patient with severe asthma; there were 9,100 white cells in the blood, with an eosinophilia of 13.5 per cent. Typhoid fever developed, the white cell count dropped to 4,700, and the eosinophiles disappeared as did the asthma. Kaplan and Rubenfeld<sup>57</sup> discuss roentgen treatment in sixty-six asthmatic patients, most of whom were thirty to fifty years of age; 72.7 per cent were relieved. They also note that:

- (a) the longer and more severe the illness, the more favorable the response
- (b) aggravation of symptoms often preceded amelioration
- (c) recurrence of attacks are unfortunately the rule rather than the exception

Despite this latter observation, roentgen therapy is definitely worth while in cases of continued asthma. Miley, Seidel and Christensen<sup>68</sup>, in eighty cases of intractable asthma, applied the Knott technique of ultraviolet blood irradiation. The patient's blood is withdrawn from a vein, citrated, and passed through a Knott hemoirradiator, a precision machine which automatically exposes the blood to strong ultraviolet energy and returns it to the venous circulation of the patient. Treatments are given every four to six weeks and then at longer intervals and finally three to four times a year. The authors state that the Knott technique was a safe and efficient method of controlling intractable bronchial asthma in forty-five of fifty-six patients who received constant treatment and observation.

The usual number of "general" papers appeared. Bray<sup>11</sup>, discussing *status asthmaticus*, advises adrenalin in suspension (not oil), ether and oil rectal enemas, aminophyllin, nicotinic acid, bronchoscopic aspirations, inhalations of CO<sub>2</sub> and steam (not oxygen), breathing exercises, and short wave therapy to the chest. Sulfonamides

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have not been successful in his hands. Prickman and Gelbach<sup>77</sup> discuss the symptomatic treatment of seasonal hay fever and asthma. Moskow<sup>70</sup>, from South Africa, occasionally gives morphine or inhalations of chloroform in acute asthma (both are dangerous). Other papers of a general nature have been written by Davison<sup>22</sup>, Rackemann<sup>83</sup>, Skinner<sup>92</sup>, and Schonwald.<sup>89</sup> Salazar Mallen<sup>65</sup> says that allergic diseases are common in Mexico City. He has examined about 3,000 patients, most of whom had "major" allergic conditions. One thousand of these were from the charity clinic at the General Hospital. Asthma and vasomotor rhinitis constituted 62 per cent of 1,687 private cases. Rackemann<sup>84</sup> has his usual excellent review of 1943 reports on allergic diseases, including asthma. Jiménez Diáz, from Madrid, gave four lectures on allergy at The Faculty of Medicine at Buenos Aires.<sup>55</sup> Among other items, he recognizes that desensitization is of little value in infectious types of asthma.

Olson, Appel and Necheles<sup>71</sup> studied a dog who had severe attacks of asthma, but autopsy revealed cardiac disease, not bronchial asthma. Red-green blindness was present in 12 per cent of Molholm's young male allergic patients<sup>60</sup>, an incidence three times higher than in normal males of that age. He believes that this possibly indicates that some cases of asthma in boys may depend in part on a sex-linked recessive factor.

The treatment of bronchiectasis is rightly swinging more and more toward lobectomy, especially in patients with a good surgical prognosis and in localities where good chest surgeons are available. All other measures, including postural drainage, bronchoscopic aspirations, chemotherapy, radiation, vaccines, and even inhalations of penicillin, have proved disappointing. The role of nasal sinusitis as a factor in producing bronchiectasis is still disputed. Recent articles on this subject have been written by Alexander<sup>1</sup>, Goodale<sup>40</sup>, Hart<sup>49</sup>, and Hinshaw and Schmidt.<sup>52</sup>

## REFERENCES

1. Alexander, J.: Role of medicine and surgery in management of bronchiectasis. *Ann. Int. Med.*, 21:565, 1944.
2. Alford, R. I.: Disposition of soldiers with bronchial asthma. *J. Allergy*, 15:196, 1944.
3. Apley, J., and Grant, G. H.: Eosinophilia with pulmonary diseases on return from tropics. *Lancet*, 2:308, 1944.
4. Applebaum, I. L.: Cerebrovascular accidents following epinephrine injections. *J. Allergy*, 15:392, 1944.
5. Ballesteros, Leopold Herraiz: Impaired nutrition in allergy. *Semana médica*, 25:5, 1944.
6. Barach, A. L.: Principles and Practices of Inhalation Therapy. Philadelphia: J. B. Lippincott, 1944. Bronchial asthma, M. Clin. N. Amer., 28:339, 1944. Physiologically directed therapy in treatment of intractable bronchial asthma. *Bull. N. Y. Acad. Med.*, 20:538, 1944.
7. Bartlett, C. L.: International Correspondence Club of Allergy, 7:77, 1943.
8. Bigler, J. A.: Allergic reactions resulting from toxoids. *J. Pediat.*, 23:241, 1943.
9. Boyd, E. F.: B. H. (Hoffman's bacillus) vaccine in allergy. *Southwest. Med.*, 27:217, 1943.
10. Brandes, W. W., Cooke, R. A., and Osborne, M. P.: Bronchiolar lymphoid hyperplasia as a cause of emphysema. *Arch. Path.*, 36:465, 1943.
11. Bray, G. W.: Allergy. *Practitioner*, 151:210, 1943.
12. Brown, E. A.: Proprietary drugs and mixtures commercially available for treatment of bronchial asthma. *Ann. Allergy*, 2:29, 1944.
13. Brown, E. A., and Goitein, P. L.: Meaning of asthma. *Psychoanalytic Rev.*, 31:299, 1944.
14. Brown, W. E., Wilder, V. M., and Schwartz, P.: A study of oils used for intramuscular injections. *J. Lab. & Clin. Med.*, 29:259, 1944.
15. Brunk, C. F.: Hypersensitivity. A neglected phase of allergy. *J. Michigan M. Soc.*, 42:808, 1944.
16. Chatterjee, S. N.: Morphine in relation to asthma. *Indian M. Rec.*, 64:35, 1944.
17. Coca, A. F.: Fundamental knowledge concerning the allergic diseases. *Ann. Allergy*, 1:120, 1943.
18. Cohen, M. B.: Bronchial asthma: Classification based on etiologic and pathologic factors. *Ann. Int. Med.*, 20:590, 1944.
19. Coke, F.: Asthma and general practitioner. *M. Press*, 210:350, 1943.
20. Cole, D. B., Nalls, W. L., and Buis, L. J.: Asthmatic atelectasis simulating pneumonia. *Virginia M. Monthly*, 71:505, 1944.
21. Cotter, L. H.: Bronchial asthma due to aluminum dust. *J. Indust. Hyg. & Toxicol.*, 25:421, 1943.
22. Davison, H. M.: The management of the asthmatic patient. *J. Nat. M. A.*, 36:45, 1944.
23. Day, G. H.: Diaphragmatic dyspnea. *J. Royal Army Med. Corps*, 81:290, 1943.
24. Deissler, K. J.: The protection of the asthmatic patient against lung irritants, with special reference to chemical agents used in warfare. *Ann. Allergy*, 2:225, 1944.
25. Deissler, K. J.: Precipitation of pulmonary edema by an overdose of antigen in a patient with rheumatic mitral disease. *Ann. Allergy*, 2:299, 1944.
26. Derbes, V. J., and Winsor, T.: Occupational allergy of respiratory tract. *Ann. Int. Med.*, 20:255, 1944.

## PROGRESS IN ALLERGY

27. Earle, K. V.: Asthma produced by ascaris infestation. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 37:451, 1944.
28. Edwards, W. M.: Diagnostic tests for atopic sensitivity. *Mil. Surgeon*, 95:222, 1944.
29. Emerson, K.: Tropical eosinophilia. *U. S. Navy M. Bul.*, 42:118, 1944.
30. Englehardt, H. T., and Derbes, V. J.: Spontaneous pneumothorax and bronchial asthma. *Ann. Int. Med.*, 21:711, 1944.
31. Feige, R., and Rosenbaum, S.: Asthmatic attacks in relation to weather. *Harefuah*, 27:80, 1944.
32. Fenner, F.: Eosinophilic leukemia and asthma. *M. J. Australia*, 2:7, 1943.
33. Field, C. E.: Spontaneous pneumothorax, massive collapse, and subcutaneous emphysema, complicating asthma. *Arch. Dis. Childhood*, 18:197, 1943.
34. Fiessinger, N., Fauvet, J., and Nick, J.: Asthma cured by typhoid fever. *Bull. et mém. Soc. Méd. du hôp. de Paris*, 58:274, 1942.
35. Figley, K. D., Wittich, F. W., Black, J. H., Petit, P. T., Sellers, E. D., Mansmann, J. A., and Prince, H. E.: Mold fungi in the etiology of respiratory allergic diseases. *Ann. Allergy*, 2:489, 1944.
36. Francis, N.: Subcutaneous emphysema during asthma. *Ann. Allergy*, 2:342, 1944.
37. French, Col. S. W., and Halpin, Major J. H.: Army allergy. *Fourth Service Command*, 1943. *Ann. Allergy*, 2:365, 1944.
38. Gay, L. N.: Personal communication.
39. Gold, E. M., and Bazemore, J. M.: The significance of allergy in military medicine. *J. Allergy*, 15:279, 1944.
40. Goodale, R. L.: *Arch. Otolaryng.*, 38:148, 1943.
41. Gray, I., and Albert, M. M.: Asthma-prevention in industry. *Indust. Med.*, 12:801, 1943.
42. Hagen, E.: Pathologic anatomic observations on surgically removed sympathetic cervical ganglia in bronchial asthma. *Deutsche Zeit. für Chir.*, 255:667, 1942.
43. Hampton, S. F., and Rand, H.: The problem of allergy at an army air forces hospital. *J. Allergy*, 15:355, 1944.
44. Hansel, F. K.: Nethamini hydrochloride and theophylline isobutanolamine in the treatment of nasal allergy and asthma. *Ann. Allergy*, 1:199, 1943.
45. Hansen-Pruess, O. C., and Goodman, E. G.: Allergic pulmonary consolidations. *Ann. Allergy*, 2:85, 1944.
46. Harkavy, J.: Vascular allergy. *J. Allergy*, 14:507, 1943.
47. Harris, A. M., and David, J. E.: Effect of ephedrin sulfate on red blood cell count in humans. *Proc. Soc. Expt. Biol. & Med.*, 54:195, 1943.
48. Harrison, T. R.: Cardiac dyspnea. *West. J. Surg.*, 52:407, 1944.
49. Hart, V. K.: Important role of bronchoscopy. *South. Med. & Surg.*, 106:167, 1944.
50. Heilig, R., and Visveswar, S. K.: Tropical eosinophilia. *Indian Physician*, 2:305, 1943.
51. Hilding, A. C.: The relation of ciliary insufficiency to death from asthma and other respiratory diseases. *Ann. Otol., Rhin., Laryng.*, 52:5, 1943.
52. Hinshaw, H. C., and Schmidt, H. W.: Some clinical problems in bronchiectasis. *Dis. Chest*, 10:115, 1944.
53. Hooker, S. B.: Qualitative differences among canine danders. *Ann. Allergy*, 2:281, 1944.
54. Horesch, A. J.: Allergy to odor of white potato (Irish potato). *J. Allergy*, 15:147, 1944.
55. Jiménez Diaz, C.: Letter. *J.A.M.A.*, 124:454, 1944.
56. Jones, S. H., and Souders, C. R.: Eosinophilic infiltration of the lungs (Loeffler's syndrome). *New England J. Med.*, 231:356, 1944.
57. Kaplan, I. I., and Rubenfeld, S.: The treatment of asthma with the Roentgen ray. *Am. J. Roentgenol.*, 50:791, 1943.
58. Karmally, A.: Cardiac asthma; its diagnosis and treatment. *M. Bull. Bombay*, 12:259, 1944.
59. Lane, S.: Psychological factors in asthma. *Bull. Menninger Clinic*, 8:76, 1944.
60. Leake, C.: International Correspondence Club of Allergy, 7:120, 1943. (Also see p. 105).
61. Leavitt, H. C.: Bronchial asthma in the functional psychoses. *Psychosom. Med.*, 5:39, 1943.
62. Leider, L. E.: Discussion of paper of French and Halpin entitled "Army allergy. *Fourth Services Command*, 1943." *Ann. Allergy*, 2:365, 1944.
63. Lima, A. Oliveira: Allergy from Timbó (Lonchocarpus). *J. Lab. & Clin. Med.*, 29:939, 1944.
64. Lowe, T. E.: Eosinophilia in tropical disease. *M. J. Australia*, 1:453, 1944.
65. Mallen, M. Salazar: Allergy in Mexico. *Ann. Allergy*, 2:433, 1944.
66. Mayer, S., Jr.: Psychogenic asthma. *Northwest. Med.*, 43:287, 1944.
67. Merrill, G. A.: Aminophylline deaths. *J.A.M.A.*, 123:1115, 1943.
68. Miley, G. P., Seidel, R. E., and Christensen, J. A.: Blood irradiations. Results in fifty cases of intractable asthma. *Arch. Phys. Therap.*, 24:533, 1943.
69. Molholm, H. B.: Association between red-green color blindness and some cases of asthma and hay fever. *J. Allergy*, 15:120, 1944.
70. Moskow, A. J.: Treatment of acute asthma. *South African M. J.*, 18:96, 1944.
71. Olson, W. H., Appel, M., and Necheles, H.: Studies on dog with severe asthmatic attacks. *Am. J. Cl. N. Path.*, 14:413, 1944.
72. Owen, Maj. J. R.: Non-tubercular pulmonary infiltrations: I. The eosinophilic lung. *Indian Physician*, 2:312, 1943.
73. Passarelli, N., Pinto de Miranda, M., and Castio, C.: Mold studies in Rio de Janeiro. *Rev. med.-cir. do Brasil*, 52:173, 1944.
74. Petersen, W. F., and Vaughan, W. T.: Weather and death in asthma. *J. Allergy*, 15:97, 1944.
75. Pirkle, H. B., and Davin, J. R.: Loeffler's syndrome. *Am. Rev. Tuberc.*, 50:48, 1944.
76. Prickman, L. E., and Gelbach, P. D.: Experience in care of asthmatic patients undergoing operation. *M. Clin. N. Amer.*, 28:991, 1944.
77. Prickman, L. E., and Gelbach, P. D.: Symptomatic treatment of seasonal hay fever and asthma. *Proc. Staff Meet. Mayo Clinic*, 19:405, 1944.
78. Prince, H. E.: Respiratory infection and bronchial asthma. *M. Rec. & Ann.*, 38:735, 1944.
79. Prince, H. E.: Mold fungi in etiology of respiratory allergic diseases. *Ann. Allergy*, 2:500, 1944.
80. Prince, H. E., and Morrow, M. B.: Mold fungi in the etiology of respiratory allergic diseases. *Ann. Allergy*, 2:483, 1944.
81. Rackemann, F. M.: Deaths from bronchial asthma. *J. Allergy*, 15:249, 1944.
82. Rackemann, F. M.: New theories concerning asthma. *New England J. Med.*, 230:284, 1944; *Med. Clin. N. A.*, 28:1082, 1944.
83. Rackemann, F. M.: Medical progress. *New England J. Med.*, 230:284, 1944.
84. Rackemann, F. M.: Allergy. Review of literature in 1943. *Arch. Int. Med.*, 73:248, 1944.

## PROGRESS IN ALLERGY

85. Randolph, T. G.: Blood studies in allergy. *J. Allergy*, 15:89, 1944.
86. Randolph, T. G., and Rawling, F. F. A.: Bronchial asthma as a manifestation of sulfonamide sensitivity. *J.A.M.A.*, 126:166, 1944.
87. Rinkel, H. J.: Food allergy. *Ann. Allergy*, 2:504, 1944.
88. Rubin, S., and Moses, L.: Electroencephalographic studies in asthma. *Psychosom. Med.*, 6:31, 1944.
89. Schonwald, P.: Recent advances in allergy. *West. J. Surg.*, 52:77, 1944.
90. Selle, W. A.: Mold fungi in the etiology of respiratory allergic diseases. *Ann. Allergy*, 2:493, 1944.
91. Shahon, H. I.: The allergic problem of the inductee, the soldier, and the veteran. *Ann. Allergy*, 2:413, 1944.
92. Skinner, N. S.: Asthma. *Nova Scotia M. Bull.*, 23:33, 1944.
93. Steele, J. M.: Evaluation of skin testing in allergy. *Ann. Allergy*, 2:17, 1944.
94. Stein, W., and Morgenstern, M.: Sensitization to thiamin hydrochloride. *Ann. Int. Med.*, 20:826, 1944.
95. Sterling, A., and Hollander, B. S.: Bronchial asthma due to sensitivity to aspidistra. *Med. Rec.*, 157:486, 1944.
96. Stoesser, A. V.: New interpretations of allergy cutaneous tests. *Journal-Lancet*, 64:145, 1944.
97. Swineford, O., Jr., and Weaver, W. M.: History-taking in allergy. *Ann. Int. Med.*, 20:293, 1944.
98. Tainter, M. L., Cameron, W. M., Whitsell, L. J., and Hartman, M. M.: *J. Pharmacol. & Exper. Therap.*, 81:269, 1944.
99. Thomas, J. W., and House, F. B.: Status asthmaticus associated with other allergies. *Cleveland Clin. Quart.*, 11:43, 1944.
100. Thomas, J. W., and Taylor, R. V.: Allergic bronchitis. *Ann. Allergy*, 1:185, 1943.
101. Tocker, A. M., and Davidson, A. G.: Relationship of bronchial asthma and hay fever to pulmonary tuberculosis. *J. Allergy*, 15:108, 1944.
102. Toomey, J. A., and Petersilge, C. L.: Dust bronchitis. *J. Pediat.*, 25:25, 1944.
103. Trowbridge, M., Jr.: Spontaneous pneumothorax complicating bronchial asthma. *Arch. Int. Med.*, 73:460, 1944.
104. Unger, L.: Annual critical survey of the recent literature on bronchial asthma. *Ann. Allergy*, 2:49, 1944.
105. Unger, L.: Bronchial Asthma. Springfield, Illinois: C. C. Thomas, 1945.
106. Unger, L.: Aminophyllin deaths. Comment on Merrill's article. *J.A.M.A.*, 124:320, 1944.
107. Vaidya, S. K.: Tropical eosinophilia. *Indian Physician*, 2:358, 1943.
108. Wasson, V. P.: Ethylene disulfonate in treatment of allergic children. *Arch. Pediat.*, 60:511, 1943.
109. Weingarten, R. J.: Tropical eosinophilia. *Lancet*, (Jan. 23) 1943.
110. Weisser, H. I.: Treatment bronchial asthma by intensive breathing therapy. *Arch. Phys. Therapy*, 25:461, 1944.
111. Yonkman, F. F., Noth, P. H., and Hecht, H. H.: Demerol. I. Pharmacologic observations. *Ann. Int. Med.*, 21:7, 1944. Noth, P. H., Hecht, H. H., and Yonkman, F. F.: Demerol. II. Clinical observations. *Ann. Int. Med.*, 21:17, 1944.
112. Zeller, M., and Edlin, J. V.: Allergy in insane. *J. Allergy*, 14:564, 1943.
113. Zink, P. L.: Mold fungi in the etiology of respiratory allergic diseases. *Ann. Allergy*, 2:502, 1944.

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8. French, S. W., and Halpin, L. J.: Army allergy: Report on allergy clinics in the Fourth Service Command. *Ann. Allergy*, 1:1, 1943.
9. Gay, L. N., Curtis, H., and Norris, T.: A pollen survey of the Islands of Bermuda. *Bull. Johns Hopkins Hosp.*, 68:179, 1941.
10. Gottlieb, Philip M., and Urbach, Erick: The distribution and pollination times of the important hay fever producing plants in the United States. *J. Lab. & Clin. Med.*, 28:1053, (June) 1943.
11. Greco, J. B., Lima, A. Olivera, and Tupinambra, A.: The pollen content of the air in Belco Horizonte, Brazil. *J. Allergy*, 13:411, 1942.
12. Gutmann, M. J.: The first report on hay fever in Palestine. *J. Allergy*, 12:182, 1941.
13. Hara, H. J.: Hay fever among Japanese: Studies of atmospheric pollen in Tokyo and Kobe. *Arch. Otolaryng.*, 30:525, 1939.
14. Hercus, C. E., and Watt, M. N.: Hay fever in New Zealand. *New Zealand M. J.*, 30:351, 1931.
15. Hlaváček, V., and Blattný, C.: Quantity of pollen in the atmosphere of Prague and its relationship to atmospheric changes. *Casop. lakt. Česk.*, 73:1021, 1934.
16. Hyde, R. W., and Kingsley, L. V.: Distribution of allergic states in selectees. *J. Allergy*, 14:386, 1943.
17. Hyde, H. A., and Williams, D. A.: A census of atmospheric pollen. *Nature*, 151:82, 1943.
18. Kalisch, A. C.: Personal interview.
19. Landau, W., and Gay, L. N.: Allergy in Germany. *J. Allergy*, 13:494, 1942.
20. Phillips, M. E.: Studies in atmospheric pollen. *Med. J. Australia*, 2:189, 1941.
21. Pirie, J. H.: Hay fever in South Africa: Its causes and treatment. *J. M. A. South Africa*, 2:374, 1928.

## REVIEW OF THE LITERATURE ON HAY FEVER FOR 1944

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In spite of the demands upon the time and energy of the profession, a goodly number of articles on hay fever have appeared in the literature this year and detailed information on this phase of allergy is to be found in several recently published books.

Gradually the importance of allergic diseases in military medicine is being recognized. Although the mobilization regulations with respect to hay fever remain the same, French and Halpin<sup>14</sup> report a definite increase in the number of cases seen. This is due mainly to the difficulty facing medical officers of the induction boards, especially in examining candidates in a non-pollen season. As stated, a "great degree of decision, diplomacy, and judgment is required to determine the fitness of a candidate and the compatibility which may or may not exist between military service and his potential degree of allergic disability."

Conferences and short courses of instruction have been given in station and general hospitals of the Fourth Service Command to stress the importance of allergy. By prompt diagnosis and treatment many allergic soldiers have been able to remain on full duty status with a minimum of time lost from training. A close degree of liaison between allergists and induction boards has brought about a more rational plan of rejection or acceptance. Since conditions of environment and diet are difficult to control in the Army, the results of therapy have not equalled those in civilian life.

Statistics from the allergy section of a station hospital in Florida given by Gold and Bozeman<sup>18</sup> also stress the military significance of allergy. These authors describe a method of preinduction consultation service for the local armed forces induction station which has proved an excellent means of eliminating allergic inductees. If hay fever symptoms are not accompanied by asthma, full duty, with preseasonal or co-seasonal desensitization therapy, is advised. If asthma is associated and is mild, the soldier is reclassified and appropriate desensitization is given.

In another article by French and Halpin<sup>15</sup> there is a summary of the findings of the allergy clinics of the Fourth Service Command for the past two years. Of a total of 32,046 allergic patients, seen in 67 clinics, 5,372 had symptoms of seasonal hay fever of sufficient severity to lead them to seek relief. Uncomplicated seasonal hay fever did not warrant a certificate of disability discharge—in only 106 cases was discharge necessary. Very good results were obtained by the use of pre-seasonal and co-seasonal therapy with the administration of pollen extract in conservative low dosages.

In the field of aviation medicine Hampton and Rand<sup>21</sup> stress the importance of a good plan of diagnostic approach. In the allergy section and clinic of a regional hospital of an aviation cadet center in Texas, from August, 1942, to August, 1943, there were 921 cases of respiratory allergy in a total of 1,238 allergic diseases. Thus, hay fever, vasomotor rhinitis and asthma accounted for three-fourths of all allergic diagnoses, with pollinosis accounting for approximately one-third of this group. According to Army regulations, issued in 1940, hay fever or any history of hay fever was disqualifying for aviation training but subsequently this was changed so that only individuals who had had hay fever two years prior to examination, regardless of past hay fever history, were disqualified. The following plan has been used to arrive at an interpretation of the degree of hay fever and the prognosis in relation to flying: as accurate a history as possible, tests with common inhalants and pollens; titration of skin sensitivity to pollen extracts; a study of nasal cytology

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and physical examination. Association with asthma is considered indicative of a severe hay fever; with eye symptoms moderate or severe; and nasal symptoms alone, as mild or moderate. A total of 283 candidates were disqualified because of allergic disorders and 135 of these because of hay fever.

Rudolph<sup>39</sup> emphasizes the importance of recognizing atypical cases of hay fever especially where significant signs and symptoms are not present in number and sequence and where seasonal limits are not definite. These conditions are often difficult to identify and are responsible for the loss of many days of active duty.

A comparative botanical survey by Lamson, et al.<sup>25</sup>, brings out the problems that arise in California, "where unlike the East, there is no extensive area in which the botany is characterized by a few identical types, it is practically impossible to find an adequate description of the botany of towns and cities, and there is a striking ignorance of the variations in flora." A comparative study is made of Barstow, California, a town at an elevation of 2,106 feet with vegetation of the desert-plain type, and Santa Ana, Calif., a coastal city at an elevation of 135 feet. Tree pollens, except for poplar and willow, are not of general significance; in the desert, grasses either do not grow or their season is so brief that they contribute little; while the coastal area has an extensive and perennial grass problem. Compositae are not the most important weeds of the desert but "salt loving" weeds are outstanding offenders. Certain prototypes are emphasized for each community and there is some overlapping, although dissimilarity is the rule.

Graphs of pollen concentrations for the Phoenix area and illustrations of common pollens are presented by Randolph<sup>36</sup> and McNeil. Their findings for the most part confirm the conclusions previously drawn by others.

Pollen surveys made by MacInnis<sup>32</sup> in South Carolina reveal that there is no month of the year when pollen is absent, there are exceptionally high pine and nut counts, especially in "good nut years," grass pollen is found during the entire year, and the ragweed season lasts longer than the usual six weeks.

From "studies on plants, pollens and patients," Brown<sup>4</sup> has found that nearly all of the seasonal hay fever in the District of Columbia is due to relatively few pollens. There is an early spring season due to tree pollens; late spring and summer due to grass and plantain; and a fall season due mainly to ragweed.

Penfound<sup>35</sup> has reported the results of six years of observation in the pollination of anemophilous trees in New Orleans. Because of the semitropical coastal climate the conditions for plant development are excellent throughout the entire year. Some species even bloom throughout the year. The initial anthesis begins five weeks earlier than at Memphis and nine weeks earlier than at Chicago. The total anthesis periods of the trees in New Orleans are almost double those of the same species in Memphis and Chicago. A given species of trees in New Orleans averages 35 days earlier than at Memphis and 63 days earlier than at Chicago. The blossoming of trees is initiated at Memphis and Chicago before the average monthly temperature reaches 45°F. whereas the lowest average mean temperature is not lower than 54.3°F. in New Orleans.

Mexico and other regions to the south of us have come in for their share of surveys. Salazar Mallen<sup>29</sup> disagrees with those who have stated that latitudes and altitudes of Mexico make pollinosis unimportant and that ragweed does not flourish in the valley of Mexico. Pollens do exist and ragweed sheds its pollen everywhere from July to September but this pollination occurs when the rainy season is heavy so that there never is more than 25 grains per square centimeter a day recorded (based on sedimentation counts). The list of pollens causing allergic respiratory symptoms includes, besides ragweed, Bermuda grass, Johnson grass, green ash, pigweed, Russian thistle, cedar tree and a few others.

In Rio de Janeiro there is only one pollen season, according to Greco and Oliveira Lima<sup>20</sup> and that is the grass season which extends from the middle of

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May to the middle of June. A minute amount of amaranth-chenopod pollen is found infrequently and has no definite seasonal character.

In a study of pollen counts in 11 Brazilian cities Greco<sup>19</sup> found grass pollen in sufficient amounts to cause hay fever, the most important grass being *Molinis minutifolia* (*capim gordura*). So far no cases of hay fever have been found among the pure natives.

Oliveira Lima and Greco<sup>20</sup> claim that there are several reasons for the rarity of pollinosis in Brazil, one being the scant interest of physicians in this subject and the other errors in diagnosis. A third factor is the low-grade sensitivity of Brazilians to the pollen of *Lithrea Moleoides*.

Molds are considered by Passarelli<sup>21</sup> to be important allergens in Rio. These commonly found are *penicillium*, *hormodendrum* and *aspergillus*. *Alternaria* is rarely seen.

Pollen and pollinosis in Argentina have been the subject of a series of articles by Herraiz-Ballester and Monticelli.<sup>1</sup> They report that the coastal variety of *Beta vulgaris* grows abundantly near Bahia Blanca in Buenos Aires. This plant, the most frequent cause of pollinosis, produces large amounts of pollen between October and the second week of December. Pollination of this chenopodiacea herb precedes or accompanies pollination of graminaceous plants. This fact is of importance in connection with therapy.

Esandi et al.<sup>11</sup>, also in Argentina, studying familial and hereditary factors in pollinosis conclude that, although symptoms may appear earlier in patients with a family history of allergy, in Bahia Blanca at least, the hereditary factor is not essential. Pollen seems to be capable of sensitizing subjects even if there is no predisposition.

*Ambrosia tenuifolia* which pollinates from November to April is the most important pollen offender in Argentina, according to Ruiz Moreno and Spegazzini.<sup>21</sup> In Buenos Aires this pollen is found only during the months of January, February and March.

Dumm and Zarate<sup>9</sup> find that *artemisia verlotorum* Lamott causes pollinosis in the city of La Plata.

Vaughan<sup>45</sup> compares the relative importance of the different plants causing hay fever in the two Americas, giving in tabular form the dates of pollination of about three dozen varieties important in the United States with comparative dates for Argentina. As great a variety of pollens are found in the different parts of South America as in the various sections of the United States, while the flora of Mexico is quite different from that of the northern part of the continent. Pollinosis should be less common in tropical than in temperate zones as more plants are pollinated by insects. Inquiries in Mexico, Central America and South America would seem to confirm this opinion.

Chobot and Dundy<sup>5</sup> studied a group of patients in the New York area who complained of hay fever and asthma from the last week of July until August 10 and whose symptoms could not be ascribed to inhalants, such as dust, feathers, or to molds; or to upper respiratory infections. The suspected pollens included Marsh elder (*Iva frutescens*), cultivated corn, wild rice and cocklebur. The problem of determining the importance of these pollens was attacked by a procedure combining positive skin tests, clinical observation for at least one season, and treatment during the following season, with a critical evaluation of the results obtained. The authors conclude that these pollens may no longer be disregarded in the New York area; they are present in the atmosphere in sufficient concentration to affect some patients and that treatment relieves symptoms.

Rogers<sup>38</sup> reports that in eastern Pennsylvania pollens other than grass and ragweed are rarely the sole cause of hay fever but they frequently complicate or act as minor synergists to the major pollens. Treatment for these minor pollens

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(English plantain in particular) is more satisfactory than it is for the major pollens.

From an Australian military hospital comes a report by Hand<sup>22</sup> of two cases of dermatitis from capeweed, one associated with symptoms of hay fever and the other with skin manifestations only. The first patient gave marked positive patch reactions and had a marked exacerbation of his dermatitis following a patch test with the flowers of capeweed but gave vegetative patch reactions to the stalk and leaf; and there were marked positive transfer reactions to capeweed flower and pollen but negative reactions to the essential oils of the capeweed plant. The patient with dermatitis only gave positive patch reactions to the capeweed flower, stalk and leaf; essential oil and pollens but passive transfer tests were negative.

Francis<sup>13</sup> believes that localized atrophy of subcutaneous fat may result not only from injections of insulin but from any type of injection regardless of the material injected. Such atrophy was observed following repeated injections of grass pollen extract in a woman who, although a diabetic, had taken no insulin for over a year.

Deissler<sup>8</sup> reports the sudden precipitation of pulmonary edema in a patient with long-standing mitral disease as a result of an overdose of pollen antigen. Respiratory distress with the expectoration of a thin pink watery fluid began twenty minutes after the injection and did not respond to the usual treatment for systemic reactions (epinephrine and aminophyllin). Prompt relief followed the injection of morphine. The patient's cardiac reserve was lowered for some time following the reaction and digitalization was necessary.

Because the incidence of asthma and hay fever is about twice as great in boys as in girls, Molholm<sup>30</sup> suggested that one of the hereditary factors upon which some cases of asthma and hay fever depend might be in part transmitted as a sex-linked recessive factor. He found in a group of 165 asthmatic male patients and 192 male hay fever patients an incidence of red-green color blindness of 8.4 per cent which is about twice as great as the incidence of about 4 per cent among unselected males.

Tocker and Davidson<sup>43</sup> find the incidence of asthma and hay fever in patients with active pulmonary tuberculosis approximately the same as in the normal population.

Reports on the use of vitamins in hay fever continue to appear. Newbold<sup>32</sup> found no evidence that ascorbic acid had any significant effect upon the allergic skin reactions due to the intracutaneous injections of short ragweed extract.

Hebald<sup>23</sup> gave a group of ten untreated hay fever patients 500 mgs. of ascorbic acid daily and weekly injections of an alkaline saline diluting fluid. The results were uniformly poor, leading to the impression that vitamin C is not an effective form of treatment for hay fever.

However, Pelner<sup>34</sup> reports that he was able to increase the tolerance of an extremely sensitive ragweed patient by the simultaneous injection of  $\frac{1}{2}$  c.c. of sodium ascorbate so that the patient was ultimately able to tolerate a dosage of 1,500 units of ragweed extract without systemic reactions.

Since edema is one of the manifestations of allergy and it also occurs in experimental animals deprived of vitamin E, Glaser and Dam<sup>17</sup> thought pollinosis might be a suitable allergic disease in which to test the use of vitamin E. Synthetic vitamin E by mouth in doses of 250 mg. per day was of no value in the treatment of a small series of cases of ragweed pollinosis.

Results of oral pollen therapy have been disappointing although occasionally a patient is found who apparently is benefited. The thought that the poor results might be due to inactivation of pollen by the digestive juices prompted Hecht, et al.<sup>24</sup>, to study the absorption of pollen from the gastro-intestinal tract. By means of passive transfer studies it was found that normal or artificially elevated

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gastric acidity decreases the absorption of orally administered pollen antigen while a reduction of acidity increases the absorption.

Because the antigenic power of grass and ragweed pollen has been shown to be diminished or abolished by gastric digestion it was thought that oral pollen therapy might be more effective if administered in enteric-coated capsules. By means of passive transfer studies, Thibierge<sup>42</sup> was able to demonstrate, in four out of fourteen nonallergic patients, the absorption of an unaltered pollen when enteric-coated capsules of grass and ragweed pollen were given.

Sherman and Barrow<sup>40</sup> studied a group of forty patients who experienced repeated constitutional reactions from injections of pollen extract to determine whether these patients exhibited an abnormal degree of reactivity in either the cutaneous or the mucosal shock tissue. The conjunctiva was used for studying mucosal reactivity and comparative titrations of the cutaneous and conjunctival reaction were made. In an experimental group of forty it was found that 50 per cent showed a reduced ratio of skin and conjunctival sensitivity. In a control group of treated patients with no constitutional reactions only 17 per cent showed a reduced ratio. The authors believe that the reduced ratio was probably the result of an excessive hypersensitivity of the mucous membranes, since there was no evidence of a diminished cutaneous reactivity.

Rockwell<sup>37</sup> describes a method for the standardization of pollen extracts as molar solutions and gives a formula for the conversion of molar concentration to molar units. Using the phosphotungstic acid precipitate only two determinations are necessary: total nitrogen and the total free a-amino nitrogen. Not only is this method considered a more accurate one for standardizing extracts, but by studying the free a-amino nitrogen it is possible to follow the aging of extracts.

Durham<sup>10</sup> compared volumetric and gravity slide methods of obtaining samples of the ragweed pollen and alternaria spore content of the air. Two totally different volumetric devices recovered practically the same amounts, whereas simultaneously exposed gravity slides caught amounts varying greatly day by day. The greatest excess catch of ragweed on gravity slides usually occurred on days of highest wind velocity but the degree of inaccuracy could not be predicted. The rates of fall for various pollen grains cannot be calculated from the rate of deposit on outdoor gravity slides because of the unavoidable impinging effect of frequent wind currents. Practical considerations will necessitate the continued use of the gravity slide method but its inaccuracy should be recognized.

Berresford and Cooke<sup>2</sup> have described a pollen dehydrator, portable and easy to operate which will dehydrate pollen to virtual completeness in a few hours. It is believed that better keeping qualities will be found in pollens rapidly and completely dehydrated.

Cooke<sup>7</sup>, in reviewing the serological studies of the hay fever type of allergies, reminds us that "we understand little of the basic facts and that there are many problems still to be solved." The positive skin test itself is not a criterion of clinical sensitiveness, and the results of treatment leave much to be desired. There are still too many problem cases; those that do not respond to injections and those in whom systemic reactions frequently recur.

Another complete review of the immunology of pollen hay fever, that of Swineford,<sup>41</sup> emphasizes the great need for a technique simple enough to permit routine office titrations of the antibody response to treatment with pollen and other extracts, and a consequent true evaluation of the role of thermostable antibody. The prompt and lasting relief afforded by the use of a heated post-treatment serum in two patients who had been unsuccessfully treated, and in another who had had no treatment give strong support to the therapeutic usefulness of the blocking antibody.

An immunologic basis for the management of hay fever patients is also stressed

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by Cohen.<sup>6</sup> He states that there is some question as to whether the thermostable antibody can explain completely the relief in treated hay fever patients but as yet it is the only mechanism that has been demonstrated which can explain the results on immunologic principles. Recently Cohen "has been working with a ragweed extract which produces good immunity but does not react with reagin and therefore produces no skin tests or constitutional reactions." With this material hay fever could be treated with a primary immunizing series of three or four doses in the first year and one dose annually thereafter.

Additional confirmation of the presence of a thermostable antibody has been given by Brown and Holden.<sup>3</sup> Since this antibody apparently binds the antigen, a passively sensitized site in which it is present requires a definite measured additional amount of antigen for neutralization.

In a continuation of her studies on the relationship between clinical hay fever and the blocking antibody, Loveless<sup>27</sup> believes that the treatment of hay fever may be shortened in those patients who have previously had a year of therapy. Twenty-four out of twenty-six patients with ragweed hay fever acquired good to excellent resistance when they were given "short booster" courses suited to their immunologic needs. Threshold tests of the conjunctiva and skin prior to the booster course gave some indications as to which subjects would give generalized reactions during therapy and tests repeated at the end of the course served as crude indices of the adequacy of therapy in newly acquired cases. Once the patient had been carried through a season of satisfactory clinical behavior, the associated levels of tolerance found in his eye, skin or serum were adopted as the goal for his future therapy. This method is still in the experimental stage "but it appears that the booster principle can be applied to the preseasonal management of pollinosis with success. It usually leads to optimal immunologic and clinical results in minimum time and without undue risk to the patient."

Gelfand and Frank<sup>16</sup> confirms the presence of a specific blocking antibody in the titre of ragweed-sensitive patients but finds that clinical results apparently do not depend upon high blocking antibody titres because the percentage of good results was identical in the patients who had low titres and those who had high titres.

A wealth of information on hay fever is presented by Urbach and Gottlieb<sup>44</sup> in their new book. Unusual is their inclusion of graphs of hay fever producing plants and pollinating trees for each of nine zones of the United States. These authors differ from most others in that they consider oral pollen therapy effective.

In Feinberg's<sup>12</sup> book a chapter on pollens and pollen allergy contributed by Durham and the discussion of allergy to fungi are excellent and of practical value to all who deal with hay fever. Mold allergy is given particular attention in response to requests of colleagues.

### REFERENCES

1. Ballesteros, Herraiz, L., and Monticelli, J. V.: Beta vulgaris variedad maritima, una cause importante y desconocida de polinosis en el sur. Beta vulgaris var. maritima, importante unrecognized cause of pollinosis in the South. *Rev. Soc. Argent. de Biol.*, 20:8, 1944. *Abst.*: *J. Allergy*, 15:51, 1944.
2. Berresford, Arthur B., and Cooke, Robert A.: A pollen dehydrator. *J. Allergy*, 15:379, 1944.
3. Brown, E. A., and Holden, Capt. Eugene A.: The presence of a thermostable inhibiting factor in the sera of patients treated for hay fever by injections of pollen extracts. *Ann. Allergy*, 2:207, 1944.
4. Brown, Grafton Tyler: Etiology of seasonal hay fever in the District of Columbia. *Ann. Allergy*, 2:197, 1944.
5. Chobot, Robert, and Dundy, Harold D.: The causes of hay fever occurring between the grass and ragweed seasons. *J. Allergy*, 15:182, 1944.
6. Cohen, Milton B.: The immunologic management of a patient with allergy. *J. Allergy*, 15:274, 1944.
7. Cooke, Robert A.: A consideration of some allergy problems. II. Serologic studies of the skin reacting allergies (hay fever types). *J. Allergy*, 15:212, 1944.
8. Deissler, K. J.: Precipitation of pulmonary edema by an overdose of antigen in a patient with rheumatic mitral disease. *Ann. Allergy*, 2:299, 1944.
9. Dumm, J. A., and Zarate, O.: La Artemisia verlotorum Lamott como un factor de polinosis en la ciudad de La Plata. *Rev. Asoc. Med. Argent.*, 58:590, 1944.
10. Durham, Oren C.: The volumetric incidence of atmospheric allergens. II. Simultaneous

## PROGRESS IN ALLERGY

measurements by volumetric and gravity slide methods. Results with ragweed pollen and alternaria spores. *J. Allergy*, 15:226, 1944.

11. Esandi, C., Ighina, D., et al.: Características de la disposición en las enfermos polinosicos de Bahía Blanca. *Dia. Med.*, 16:560, 1944.
12. Feinberg, Samuel M.: *Allergy in Practice*. p. 798. Chicago: The Year Book Publishers, Inc., 1944.
13. Francis, Nathan: Localized atrophy of subcutaneous fat after repeated injections of grass pollen. *Ann. Allergy*, 2:344, 1944.
14. French, Col. Sanford W., and Halpin, Capt. Lawrence J.: The military management of allergic diseases. *J. Iowa M. Soc.*, 54:272, 1944.
15. French, Col. Sanford W., and Halpin, Major Lawrence J.: Army allergy—Fourth Service Command, 1943. *Ann. Allergy*, 2:365, 1944.
16. Gelfand, H., Harold, and Frank, D. Edward: Studies on the block antibody in serum of ragweed treated patients. II. Its relation to clinical results. *J. Allergy*, 15:332, 1944.
17. Glaser, Jerome, and Dam, Henrik: Failure of vitamin E in the treatment of ragweed pollinosis (hay fever). *J. Allergy*, 15:18, 1944.
18. Gold, Major Edwin M., and Bozemore, Capt. James M.: The significance of allergy in military medicine. A report of the incidence of allergic diseases in a large station hospital and a method of pre-induction evaluation of the allergic state. *J. Allergy*, 15:279, 1944.
19. Greco, J. B.: Pollen studies in Brazil: Pollen counts in eleven Brazilian cities. *Rev. Med.-Cir. do Brasil*, 52:104, 1944.
20. Greco, J. B., and Lima, A. Oliveira: The pollen count of the air in Rio de Janeiro, Brazil. *J. Allergy*, 15:138, 1944.
21. Hampton, Major S. F., and Rand, Capt. H.: The problem of allergy at an army air forces hospital. I. Respiratory allergy (hay fever vasomotor rhinitis and bronchial asthma). *J. Allergy*, 15:355, 1944.
22. Hand, Lt. Eugene A.: Contact dermatitis due to capeweed. *Arch. Dermat. & Syph.*, 49:331, 1944.
23. Hebard, S.: Clinical evaluation of ascorbic acid in the treatment of hay fever. *J. Allergy*, 15:236, 1944.
24. Hecht, R., Mosko, M. M., Lubin, J., Sulzberger, M. B., and Baer, R. L.: The absorption of whole ragweed pollen from the gastro-intestinal tract. *J. Allergy*, 15:9, 1944.
25. Lamson, R. W., McMichael, H., and Stickler, M.: Potential pollinosis in a desert and a coastal city. A comparative botanic survey of Barstow and Santa Ana, California. *J. Allergy*, 15:21, 1944.
26. Lima, A. Oliveira, and Greco, J. B.: Alergia polinica en Brazil. (Pollen allergy in Brazil). *Brasil Med.*, 57:371, 1943.
27. Loveless, Mary Hewitt: Immunologic studies of pollinosis. VI. Shortening the treatment of hay fever. *J. Allergy*, 15:311, 1944.
28. MacInnis, Katharine Bayliss: Pollen counts 1941-1943, Columbia, S. C. *J. South Carolina M. A.*, 40:77, 1944.
29. Mallen, Mario Salazar: Allergy in Mexico. *Ann. Allergy*, 2:433, 1944.
30. Molholm, Hans B.: An association between red-green color blindness and some cases of asthma and hay fever. *J. Allergy*, 15:120, 1944.
31. Moreno, G. Ruiz, and Spiegazzini, R.: Geographic distribution of ambrosia tenuifolia in Argentina. *An. d. Inst. Invest. Fis. Apl. a la Pat. Humana* 5:153, 1943. *J. Allergy*, 15:51 (Allergy Abstr.), 1944.
32. Newbold, H. L.: The relationship between spontaneous allergic conditions and ascorbic acid. An experiment employing skin tests and ascorbic acid on subjects with hay fever. *J. Allergy*, 15:385, 1944.
33. Passarelli, N., Pinto de Miranda, M., and Castro, C.: Cogumelos do ar na cidade do Rio de Janeiro (Mold studied in Rio de Janeiro). *Rev. Med.-Cir. do Brasil*, 52:173, 1944.
34. Peiner, Louis: The importance of vitamin C in bodily defenses. I. The anti-anaphylactic effect of vitamin C in the prevention of pollen reactions. *Ann. Allergy*, 2:231, 1944.
35. Penfound, Wm. T.: Pollination of anemophilous trees in New Orleans. *Ann. Allergy*, 2:315, 1944.
36. Randolph, Howell, and McNeil, Margaret: Pollen studies of the Phoenix area. *J. Allergy*, 15:125, 1944.
37. Rockwell, George E.: The molar standardization of ragweed pollen extracts. *Ann. Allergy*, 2:137, 1944.
38. Rogers, Harry L.: Sensitivity to minor pollens. *Ann. Allergy*, 2:125, 1944.
39. Rudolph, Capt. Jack: Atypical allergic manifestations; their identification and treatment. *Mil. Surgeon*, 95:52, 1944.
40. Sherman, Hyman, and Barron, Bessie: Studies in hypersensitivity of the mucous membranes. V. Comparative studies of skin and ophthalmic reactions in hay fever patients presenting constitutional reactions. *J. Allergy*, 15:165, 1944.
41. Swineford, O., Jr.: Observations on the immunology of pollen hay fever; A critical review. *South. M. J.*, 37:342, 1944.
42. Thibierge, Narcisse F.: Absorption of pollen extracts from the alimentary tract. *J. Allergy*, 15:298, 1944.
43. Tocker, Albert M., and Davidson, Alexander G.: The relationship of bronchial asthma (and hay fever) to pulmonary tuberculosis. *J. Allergy*, 15:108, 1944.
44. Urbach, Erich, and Gottlieb, Philip M. *Allergy*, p. 1073. New York: Grune and Stratton, 1943.
45. Vaughan, W. T.: Alergia en el nuevo mundo. (Allergy in the new world). *Dia. Med.*, 16:54, 1944.

## \* *In Memoriam* \*

### **AARON BROWN**

On January 24, 1945, Dr. Aaron Brown died very suddenly of a heart attack in New York City at the age of sixty-one years. Doctor Brown was not a member of the College but he was a very tolerant individual who loved people and was willing to be of assistance to any physician in any way within his power and this was considerable because of his wide circle of intimate friends in all fields of medicine all over the country. Although an individual who was in no way aggressive, he was an intelligent, far-sighted physician. During his presidency of the Society for the Study of Asthma and Allied Conditions he had appointed committees and attempted to set in motion the machinery for carrying out many progressive ideas for the advancement of allergy which eventually reached their fulfillment years later when the American College of Allergists was organized, and subsequently also in the American Academy of Allergy when this was formed by the merger of the two older national societies.

Dr. Aaron Brown was the chief allergist of the New York University Medical School clinic, assistant attending physician at Bellevue Hospital, assistant clinical professor of medicine at New York University, consulting physician at the Bronx Hospital, and director of the allergy service at the Midtown Hospital of New York City. His membership included the American Association of Immunologists, the American Association for the Study of Allergy, the Society for the Study of Asthma and Allied Conditions, the American Therapeutic Society, the New York Academy of Medicine, the American Association for the Advancement of Science and the American Academy of Allergy. He was an honorary member of Sigma Xi.

Scientifically, Doctor Brown is probably best known for his popularization of the perennial method for the treatment of pollinosis which was original with him although it had possibly been thought of by others who did not develop the procedure as thoroughly as Doctor Brown. Besides his numerous scientific investigations, he was intensely interested in the practical aspects of allergy, and originated among many others such simple and effective ideas as the use of different colored rubber stoppers to indicate different types of solutions, and the "Aaron Brown tourniquet" which consists simply of the application of a snug-fitting ordinary rubber band above the site of the injection of an allergen extract in order to slow down absorption and ward off generalized reactions in individuals susceptible to these.

In the passing of Aaron Brown most of us have lost a beloved friend and all of us have lost an enthusiastic and helpful co-worker. The American College of Allergists is pleased to honor him with this memorial.

JEROME GLASER

### **ALFRED M. GOLTMAN**

Dr. Alfred M. Goltman of Memphis, Tennessee, a charter member of the American College of Allergists, died November 11, 1944, at the age of 49. He was born at Nanticoke, Pennsylvania. He received his M.D. degree from Columbia University College of Physicians and Surgeons in 1921. Doctor Goltman received his training in allergy at the Balyeat Hay Fever and Asthma Clinic, Oklahoma City, Oklahoma. He had done considerable investigative work on molds for the government in the state of Tennessee and on botanical aspects of hay fever in the

## IN MEMORIAM

Memphis area. He was a member of the staffs of Baptist Memorial Hospital, John Gaston Hospital and Memphis Eye, Ear, Nose and Throat Hospital. Doctor Goltzman was Associate Professor of Medicine at the University of Tennessee. His publications included the following subjects: "Studies in Allergy," "The Mechanism of Migraine," "Unusual Cases of Migraine with Special Reference to Treatment," "Diabetes Mellitus as a Factor in Intractable Asthma," "Migraine," "Allergic Headache."

He is survived by his wife, Helen Hirsch Goltzman, and twin daughters, Peggy and Jean.

Doctor Goltzman was modest and retiring, sincere, and an enthusiastic member of the College. We mourn his loss.

FRED W. WITTICH

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### HARRY IKER

Mr. Harry Iker, of Chicago, Illinois, died on February 19, 1945, at the age of forty-eight, as a result of coronary disease. He was born in East St. Louis, Illinois, on September 2, 1896. He was actively interested in pharmacy in which he held a degree. In 1932 he began the manufacture of hypo-allergenic encasings and became interested in allergy at the same time. An important part of this work included environmental surveys of patients' homes for physicians.

In 1939 he published the first of his many abstracts of interest to allergists and joined the International Correspondence Club of Allergy. When the American College of Allergists was organized, he was made a charter member and became the only lay Fellow (Associate) in that organization, a distinct honor in itself. He was also a member of the American Pharmaceutical Association and the American Association for the Advancement of Science. At the time of his death he was engaged in the compilation of a reference text concerning items of interest in allergy.

In 1919 he married Rose Weiner. He has two sons in the Armed Forces, Lt. Charles S. Iker of the Infantry, just returned from the Pacific, and Pvt. Howard Iker of the Infantry, now somewhere in Germany.

Harry Iker was a tireless worker whose untimely passing is keenly felt by his many friends in the profession.

MICHAEL ZELLER.

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### Severe Light Hypersensitivity Cured by Cholecystectomy

(Continued from Page 128)

17. Thurmon, F. M.: Hydroa estivale: A successful treatment. Section on Dermatology, A. M. A., Atlantic City, June 12, 1942.
18. Urbach, E.: Schwerste Lichtdermatosen auf Grundlage von isolierter pathologischer Porphyrinbildung im Darme infolge Dysbakterie und Hepatopathie. Klin. Wchnschr., 17:304, 1938.
19. Urbach, E., with the collaboration of Gottlieb, P. M.: Allergy. New York: Grune and Stratton, 1943.
20. Urbach, E., and Bloech, J.: Hydro vacciniforme, Porphyrinopathie, Hepatopathie. Wien. klin. Wchnschr., 47:527, 1934.
21. Vannotti, A.: Porphyrin und Porphyrinopathien. Berlin: Julius Springer, 1937.

## News Items

Dr. John A. Kolmer, Philadelphia, has recently been elected to Honorary Fellowship in the American College of Allergists in recognition of his high attainment in the science of immunology and allergy.

Announcement has been made that Commander M. C. Harris has been released from Naval duty and will resume his practice of allergy at 133 East 58th Street, New York City, beginning April 15, 1945.

The College has just received its second installment for \$500 which is the second grant to the American College of Allergists toward "The Marcelle Research Fund." This fund is being applied to the Fellowship established with the Mayo Foundation under the direction of Dr. Charles F. Code for research in allergy.

Dr. G. Estrada de la Riva, Havana, Cuba, has been promoted to Active fellowship in the College. Doctor de la Riva, who is a member of the Editorial Staff of the *ANNALS OF ALLERGY*, has been responsible for abstracting the scientific articles which appear in the *ANNALS* and translating them into Spanish. These abstracts appear in supplement form and are sent to all the Spanish-reading members of the College and other leading allergists in the South and Central American countries and Cuba, who request them.

At the meeting of the Chicago Society of Allergy, held at the Illinois Athletic Club, February 19, Dr. Steven O. Schwartz presented a paper entitled "The Prognostic Significance of Bone Marrow Eosinophiles in Thrombocytopenic Purpura," by invitation, and Dr. Theron Randolph discussed "The Blood Response Following Trial Injection of Food in Allergic Subjects."

At the Seventh Annual Forum, held at Pittsburgh, January 26, Dr. Mary Loveless received the first Marcelle Award of \$350 for her contributions on the role of the thermostable antibody when determining the clinical response in hay fever. Dr. Charles F. Code, of the Mayo Foundation, received the second Marcelle Award of \$150 on the mechanism of anaphylactic and allergic reactions with an evaluation of the role of histamine in their production. Dr. Arnold Rich and his associates, of Johns Hopkins Medical School, received honorable mention for their studies on serum sickness and periarthritis nodosa. Dr. Frank Simon, of Louisville, also received honorable mention for his observations on human dander in relation to allergy. Dr. Milton J. Rosenau, Professor of Epidemiology, University of North Carolina, received the annual gold medal.

On March 8, at the Annual Doctors' and Wives' Banquet, sponsored by the Spokane County Medical Society, Spokane, Washington, Dr. Herbert J. Rinkel of Kansas City presented "The Etiology of Hay Fever" in Kodachrome stills, following which he presented his outstanding color film "The Symphony of the Seasons." On March 9, at a luncheon meeting of the Society, he discussed "The Diagnostic Problem in Seasonal Hay Fever," and at an evening meeting the same date he presented "Food Allergy."

On March 12, at Vancouver, Washington, Doctor Rinkel presented a combined lecture on "Hay Fever" and "Food Allergy" before the Vancouver County Medical Society.

## NEWS ITEMS

On March 18, he spoke before the Pueblo, Colorado, physicians and their guests concerning "The Treatment of Seasonal Hay Fever" and "The Nature and Mechanism of Food Allergy."

The Southwest Allergy Forum met April 9 and 10 at the Jung Hotel, New Orleans. Although owing to war restrictions the registration was necessarily limited, there was no lack of enthusiasm, and the traditional Southern hospitality promoted informal cordial fellowship.

There were numerous round-table discussions on all phases of allergy, formal presentations of papers and luncheon discussions of timely topics in which anyone could participate.

Among the speakers were Dr. Albert V. Stoesser, who presented the experiences of his staff with "Status Asthmaticus and Pitressin Therapy"; Dr. Coyne Campbell, who gave a most interesting paper on "A Brief Critique of Psychosomatics" in which allergic problems are discussed; Dr. Herbert J. Rinkel, who presented "Migraine"; Dr. Louis Brunsting, who presented "Dermatology as Related to Allergy," and Dr. William F. Petersen, who gave a fascinating talk on "Weather as It Affects the Normal and the Allergic Individual." Doctor Petersen was also guest speaker at the Monday evening dinner.

The leaders of round tables were: Drs. Henry D. Ogden, Jonathan Forman, Homer E. Prince, Fred W. Wittich and L. O. Dutton.

Dr. Ralph Bowen was chairman of the Executive Committee, and Dr. B. G. Efron, chairman of the Committee on Arrangements.

### INSTRUCTIONAL COURSES AVAILABLE

Sets of the complete intensive instructional courses covering all phases of important allergic diseases, presented at St. Louis, November 4 to 8, inclusive, are now available. They include comprehensive outlines and lectures including tables, figures, diets, prescriptions, etc., with space for additional notes.

Subjects and authors are listed below:

- Dermatologic Allergy—Rudolf L. Baer, M.D., New York, N. Y.
- The Physiologic and Immunologic Aspects of Allergy (Illus.)—F. W. Wittich, M.D., Minneapolis, Minn.
- The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses—French K. Hansel, M.D., St. Louis, Mo.
- Some Neurologic and Psychologic Aspects of Allergy—Michael Zeller, M.D., Chicago, Ill.
- Food and Digestive Allergy (Illus.)—Herbert J. Rinkel, M.D., Kansas City, Mo.
- Allergy of the Central Nervous System—T. Wood Clarke, M.D., Utica, N. Y.
- Drug Allergy—Jonathan Forman, M.D., Columbus, Ohio.
- Pediatric Allergy—Ralph Bowen, M.D., Houston, Texas.
- Allergy Elimination Diets for Children, Albert V. Stoesser, M.D., Minneapolis, Minn.
- Mold Allergy (Illus.)—Homer E. Prince, M.D., Houston, Texas.
- Bronchial Asthma—Leon Unger, M.D., Chicago, Ill.
- Physical Allergy—Cecil M. Kohn, M.D., Kansas City, Mo.

The price of the complete set is \$3. Please mail your check with your order.

AMERICAN COLLEGE OF ALLERGISTS  
401 La Salle Medical Building  
Minneapolis 2, Minnesota

## BOOK REVIEWS

**BRONCHIAL ASTHMA.** By Leon Unger, M.D., Assistant Professor of Medicine, Northwestern University Medical School, Chicago. Introduction by Morris Fishbein, M.D., Editor, *Journal of the American Medical Association*. 724 pages. 126 figures. One color plate. Price \$9.00. Springfield: Charles C. Thomas, 1945

The book is clearly written for the medical student, general practitioner, specialist and patient and is the most complete single text on bronchial asthma at the present time. The text is divided into three sections. A clinical section comprises by far the greater part of the book. This is followed by a laboratory section and an appendix.

The clinical section contains seventeen chapters. The etiology, diagnosis and treatment of bronchial asthma are emphasized. The author's long years of teaching and extensive clinical practice have particularly fitted him to write a sound textbook on the subject. Theoretical considerations are omitted, without sacrificing the known principles of allergic diseases. Prevention of asthma in children is adequately discussed, as well as an important "Military" chapter, which will assist in the selection and rejection of allergic individuals and in treating those already in the Service.

The laboratory section is devoted to the technique of preparing extracts used for diagnosis and treatment, the technique of pollen and mold counts and special procedures.

The appendix lists the sources of allergens and instructions regarding diets and avoidance of house dust and other excitants. There are detailed instructions for patients which are of considerable practical value, with an alphabetically arranged list of patent medicines for the treatment of asthma, most of which have been analyzed by the Bureau of Investigation of the American Medical Association, and the individual references are noted.

Throughout the book, it is refreshing to see unbiased references and the omission of unimportant assertions of priorities and without belittling fundamental concepts of our present-day knowledge of the allergic reactions, which is manifest in some of our recent textbooks on the subject.

The student, practitioner and specialist will find himself referring to this book more and more.

F.W.W.

**THE 1944 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY.** By Marion B. Sulzberger, M.D. and Rudolf L. Baer, M.D. 544 pages. 75 illustrations. Price \$3.00. Chicago: The Year Book Publishers, 1944.

In line with WPB restrictions, the publishers continue the same format as the 1943 Year Book. It is a compact handbook, durably bound; the illustrations are clear, and the size of the print for the text and references make it very easy reading.

This book just off the press is packed with 147 new treatments and new proved therapeutic ideas, with additional diagnostic procedures. The unusual experience of the authors with the many skin problems encountered in Military life is incorporated in this volume with up-to-date guidance to more than 150 disease conditions. It is a combination of the clinical findings of dermatologic processes the past twelve months with a critique of nearly 400 leading articles selected from eighty-one clinical publications of this country and thirteen other countries. All positive advances are included with expertly selected illustrations. The information is so arranged that it can be very easily assimilated and easily referred to.

Penicillin therapy of syphilis, sulpha therapy of skin diseases, prophylaxis and

## BOOK REVIEWS

treatment of chancroid, technique of low voltage x-ray therapy of five types of skin lesions, the practical details of industrial, Military, and Naval dermatology, burns therapy and the Navy's new five-hour treatment for scabies are just a few practical points selected from this Year Book. No dermatologic condition seems to have escaped ample consideration by the authors. The formalin treatment of warts, the differentiation of benign and malignant moles, important advances in immunology of dermatologic, venereal and other infectious diseases are adequately presented. The authors include a complete practical guide for skin tests, including patch tests, allergens for patch testing, scratch tests and the intracutaneous test. There are tables of common eczematogenic allergens and common urticariogenic allergens for differential diagnostic scratch testing together with an evaluation of tests. Improved prescriptions and dermatologic therapy in the tropics receive special attention. All of these make this compact manual of skin diseases an extremely useful ready reference for any doctor's office.

F.W.W.

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**A MANUAL OF ALLERGY LECTURES FOR NURSES.** By James A. Mansmann, M.D. 32 pages, with outlines, figures and space for notes. Price, 75 cents. Pittsburgh: University of Pittsburgh Bookstore, December, 1942.

The author is lecturer in allergy at St. Francis, Pittsburgh, and Homestead Hospital Nursing School. He is instructor in allergy at the University of Pittsburgh Medical School. Doctor Mansmann's experience in teaching nurses in this specialty qualifies him to prepare an authoritative Manual which is a comprehensive outline of accepted routine procedures in the diagnostic approach and management of allergic diseases to be encountered by nurses during their training and when in private practice.

It is an excellent manual, designed for the nurse with a knowledge of the medical basic sciences and attempts to correct the objections and difficulties of following a course of lectures without any text.

The Manual covers seven to ten hourly lectures and is augmented by demonstrations of skin testing, pollen grains and counts, "dust free" bedrooms and other avoidance and elimination measures. The author assumes that the nurse has had very little contact with this specialty and in all probability an incorrect knowledge gathered from lay sources. Doctor Mansmann prepared the Manual, "hoping the nurse in the future can give the allergic patient intelligent care and helpful suggestions. The allergic patient often depends upon the nurse for correct information." He has succeeded in presenting the essentials for this important instruction so that any lecturer on allergy to nurses will find it of valuable assistance.

F.W.W.

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**ESSENTIALS OF ALLERGY.** By Leo H. Criepp, M.D., Assistant Professor of Medicine and Lecturer in Immunology, School of Medicine, University of Pittsburgh; Consultant in Allergy Medical Service of the U. S. Veterans Administration, with a foreword by Robert A. Cooke, M.D., Chairman, Committee on Education, American Academy of Allergy. 381 pages. 42 illustrations. 1 color plate. Price \$5.00. Philadelphia: J. B. Lippincott Co., 1945.

The author, with extensive experience in the teaching of immunology and allergy, is particularly fitted to prepare a manual on allergy for the medical student and for the general practitioner.

There are seventeen chapters covering the various phases of allergy, including the diagnosis and treatment of the various allergic diseases, with a special chapter on allergy in children and a final chapter describing the various diagnostic skin tests. The excellent bibliographies of available material following each chapter indicate the thoroughness with which the author has prepared the manual. In the main, the author adheres to the orthodox teaching of allergy.

## BOOK REVIEWS

The manual is clear and concise. It is excellent for the student of allergy during his undergraduate course, as well as for the general practitioner. F.W.W.

**OUTLINE OF THE AMINO ACIDS AND PROTEINS.** By Melville Sahyun, M.A., Ph.D., 251 pages. Numerous illustrations and figures. Price \$4.00. New York: Reinhold Publishing Corporation, 1944

The editor, Vice President and Director of Research, Frederick Stearns and Company, was assisted by twelve contributing authors who hold prominent teaching positions in the departments of Biochemistry of leading medical schools in the United States. There is a foreword by Carl L. A. Schmidt, of the Department of Biochemistry of the University of California.

The authors have succeeded in simplifying in one easily read volume the essentials of the chemistry and biochemistry of amino acids and proteins. They intentionally refrained from the controversial aspects of this difficult subject, but recite references to larger treatises dealing with protein chemical structure, their relationship to immunologic reactions, theories of denaturation, detoxication and other theoretical aspects.

There are eleven chapters, each leading with a photograph of a pioneer who has made fundamental contributions to this important subject. These are accompanied by a brief account of the development of the chemistry and behavior of the proteins and amino acids. Both industry and medicine have awakened to the great importance of proteins and amino acids. Each chapter is followed by a very complete bibliography. There is also a list of general references.

The book furnishes excellent basic knowledge necessary for a clearer concept of the metabolism and functions of the amino acids and for a clearer understanding of their nutritional significance. The last chapter deals with amino acids and proteins in nutrition with a classification of the amino acids with respect to their growth effects, as well as a list of the minimum amount of each essential amino acid necessary to support normal growth when known essentials are included in the food. With our recent knowledge of the important role which globulins play in antibody formation, the chapter on "Relation of Amino Acids and Their Derivatives to Immunity" becomes of special interest to immunologists and allergists.

The book furnishes excellent basic knowledge to the student of the subject as well as the physician in practice. F.W.W.

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**CLINICAL ACTIONS OF ETHYLNORSUPRARENIN (Butanefrine)** M. L. Tainter, M.D., W. M. Cameron, M.D., L. J. Whitsell, M.D., and M. M. Hartman, M.D. *J. Pharmacol. & Experimental Therapeutics*, 81:269 (July), 1944.

Ethylnorsuprarenin, a new companion drug to epinephrine, has been tried in acute and chronic asthma in patients ranging from three to sixty-four years. Chemically it is 1-(3, 4 dihydroxyphenyl)-2-amino-1-butanol, a colorless, odorless, crystalline powder with a bitter taste, readily soluble in water. Administration was effected subcutaneously, intramuscularly and intravenously. The pressor effects of epinephrine were absent, the diastolic pressure actually being lowered, and the excitant effects on the central nervous system were absent or minimal. Bronchi were effectively relaxed. Doses ranged from 0.2 to 2 mgm. Compared to epinephrine, there was less nausea and vomiting in children and no precordial pain in the older age groups with cardiovascular disease. In general, tremor, nervousness and excitement were either absent or less pronounced than with epinephrine. 50 to 100 per cent larger doses than with epinephrine were required to produce comparable relief.

M.M.H.

NOTE: Ethylnorsuprarenin has been referred to as Butafrine and may be again in the future.